EFFECT OF KETAMINE ON PATIENTS WITH MODERATE TO SEVERE DEPRESSIVE DISORDER

A THESIS SUBMITTED TO

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT (PUNJAB)

IN THE PARTIAL FULFILLMENT

FOR THE AWARD OF DEGREE OF

DOCTOR OF MEDICINE

IN

PSYCHIATRY

2024

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Dedicated

to

my Family

&

Teachers

ACKNOWLEDGEMENT

First and foremost, I extend my deepest gratitude to the Almighty for His gracious blessings and the strength imparted to accomplish this work. As this project reaches its successful culmination, I reflect on the journey and recognize the unwavering support and blessings from many individuals.

I owe my profound gratitude to my guide, mentor, and supervisor, **Dr. Ranjive Mahajan**, *Former Professor and Head, Department of Psychiatry, Dayanand Medical College and Hospital, Ludhiana. His unwavering support and mentorship have been instrumental in my academic and professional growth since my post-graduation days. Dr. Mahajan's clarity of thought, ability to simplify complexities, and dedication to the highest standards have greatly influenced my approach to psychiatry and life. This dissertation was made possible due to his affable demeanor and encouraging guidance. I remain forever grateful for his wisdom, support, and care.*

I extend my special thanks to my esteemed teacher, **Dr. Navkiran S. Mahajan**, *Professor and Head, Department of Psychiatry, Dayanand Medical College and Hospital, Ludhiana. Her invaluable guidance, keen interest, and sincere efforts have*

been pivotal throughout the course of my study. Dr. Navkiran's prompt inspiration, timely suggestions, and dynamic approach enabled me to complete my thesis.

I am privileged to express my gratitude to my co-supervisor, **Dr. P.L. Gautam**, Professor and Head, Department of Critical Care Medicine, Dayanand Medical College and Hospital, Ludhiana. His immense knowledge and wisdom have been a guiding light throughout my study, particularly in providing assistance with the infusion sessions.

I extend my heartfelt thanks to the consultants of the Department of Psychiatry, **Dr. Pankaj Kumar** and **Dr. Mitthat Miglani,** for their expert guidance and support during times of need.

I am sincerely grateful to my senior residents **Dr. Gabby Sethi** and **Dr. Cherry Sikka**, ex-senior residents **Dr. Nikhil Gautam** and **Dr. Mantaz Dhillon**, as well as seniors **Dr. Aarti gupta** and **Dr. Ardaas Sandhu** for their constant support and encouragement throughout this project.

Words cannot adequately express my gratitude to my parents, **Mr. Kuldeep Singh Duggal** and **Mrs. Balbir Kaur Duggal**, for their unwavering support and continuous encouragement throughout the

tenure of my research project. I pray for the strength and capability to fulfill their dreams.

I am also thankful to my co-PGs, **Dr. Sandeep Kaur Dhillon** *and* **Dr. Alisha Aluna**, *my juniors,* **Dr. Shagufa Ali, Dr. Rakshanda Vashisht, Dr. Kimi Garg, Dr. Prince Jindal, Dr. Harmanjot Singh**, *and* **Dr. Robin Singla**, *for their immense cooperation and support.*

I am deeply appreciative of my friends, **Dr. Khushneel Baath, Dr. Akashdeep Singh Sohi, Dr. Faazal Singh Sangha, Dr. Paramveer Singh** *and* **Dr. Bhawna Budhiraja** *for providing the moral and emotional support needed to complete my thesis.*

I am extremely thankful to **Baljeet Kaur, Gurinder Mangat** *and* **Jagjeet Singh** *for their valuable assistance.*

Lastly, but most importantly, I am indebted to all the patients for their cooperation, which was essential for the completion of this work.

Dr. Nitin Baldeep Singh Duggal

LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
BDI	Beck depression inventory
BDNF	Brain-derived neurotrophic factor
BPRS	Brief psychiatric rating scale
CDCP	Centers for disease control and prevention
CDAP	Chronic disease action plan
CADSS	Clinician-administered dissociative states scale.
DSM-5	Diagnostic and statistical manual of mental disorders, fifth edition
DSM-IV	Diagnostic and statistical manual of mental disorders, fourth edition
DLPFC	Dorsolateral prefrontal cortex
ECT	Electroconvulsive therapy
ESKET	Esketamine
FGF-1	Fibroblast growth factor-1
GABA	Gamma aminobutyric acid
GAD-7	Generalized anxiety disorder-7
GWAS	Genome-wide association studies
GDS-SF	Geriatric depression scale-short form gds-sf
GT	Glutamate transporter
GRADE	Grading of recommendations, assessment, development, and evaluations
HAM-D	Hamilton depression rating scale
HDRS	Hamilton depression rating scale
HPA	Hypothalamic–pituitary–adrenal axis
IGF-1	Insulin-like growth factor-1

IL-6	Interleukin-6
IM	Intramuscular
IV	Intravenous
KET	Ketamine
MDD	Major depressive disorder
MDEs:	Major depressive episodes
mTOR	Mammalian target of rapamycin
MAOI	Monoamine oxidase inhibitors
MADRS-SI	Montgomery-åsberg depression rating scale suicide item
MADRS	Montgomery-åsberg depression rating scale.
NMDAR	N-methyl-d-aspartate receptors
NE	Norepinephrine
OCD	Obsessive compulsive disorder
PHQ-9	Patient health questionnaire-9
PTSD	Post traumatic stress disorder
PFC	Prefrontal cortex
PCL-5	PTSD checklist for DSM-5
QIDS-SR	Quick inventory of depressive symptomatology - self-report
RCT	Randomised controlled trial
RDT	Rapid-acting dissociative therapy
SSI	Scale for suicidal ideation
SSRI	Selective serotonin reuptake inhibitors
SERT	Serotonin transporter
SKY-D	Study of ketamine for youth depression
SL	Sublingual

TRD	Treatment resistant depression
TCAs	Tricyclic antidepressants
TNF-α	Tumour necrosis alpha
VAS	Visual analog scales
AMPARs	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors

ABSTRACT

Introduction: Major depressive disorder (MDD) is a debilitating condition marked by a depressed mood, diminished interests, impaired cognitive function, and vegetative symptoms. Recent evidence shows that a single sub-anesthetic dose of ketamine administered intravenously or intramuscularly, can rapidly enhance the antidepressant effects of SSRIs in treating MDD.

Aim of Study: To compare the therapeutic efficacy of ketamine administered intravenously versus intramuscularly in patients with MDD.

Materials & Methods: This one-year randomized controlled trial in the Department of Psychiatry at DMC&H, Ludhiana, involved 90 inpatients aged 18-65 with MDD diagnosed per ICD-11. Participants, on Escitalopram (10-20 mg) for atleast four weeks, were randomly assigned to three groups of 30 patients each after providing informed consent. Group A received intravenous ketamine, Group B received intramuscular ketamine, and Group C was the control group. Sociodemographic data were collected, and depression severity was measured using the Montgomery-Åsberg Depression Rating Scale (MADRS).

Results: The MADRS scores in both IM and IV groups showed a statistically significant improvement from baseline to 4 hours post-infusion across all four KET sessions ($p < 0.05$). In the IM group, there was a 47.04% reduction in MADRS scores (17.78 points) from baseline to the final session. In the IV group, there was a 48.69% reduction (21 points) from baseline to the final session.

Conclusion: Our study found that ketamine, administered at 0.5 mg/kg intramuscularly and intravenously, is safe and effective, rapidly decreasing depressive symptoms within hours, as measured by MADRS. Both IV and IM ketamine led to significant improvements 4 hours after a single dose, maintained with subsequent doses over two weeks. No significant difference was observed in the reduction of mean MADRS scores between the IM and IV groups at each session.

Keywords: Major depressive disorder, Ketamine, Therapeutic efficacy, Randomised controlled study, intravenous versus intramuscular, MADRS

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INTRODUCTION

Depression is a chronic mental health condition that impacts 300 million individuals globally. Symptoms include low energy, disinterest in daily activities, psychomotor agitation, difficulty concentrating, suicidal thoughts, excessive sleeping, impaired social functioning, and reduced appetite[1]. Major Depressive Disorder (MDD) is about twice as common in women as in men, affecting one in six adults during their lifetime. MDD ranks as the second highest contributor to chronic disease burden, measured by 'years lived with disability[2]. It is also associated with an increased risk of developing additional conditions such as diabetes, heart disease, and stroke, which further amplify its overall disease burden[3]. Moreover, MDD can result in suicide, with up to 50% of the 800,000 annual suicides occurring during a depressive episode[4]. Patients with MDD have nearly a 20-fold increased risk of dying by suicide compared to the general population[5].

Depression impacts 15.7 million adults aged 18 and older in the United States and is the target of substantial prevention and treatment efforts. In 2008, the World Health Organization ranked depression as the third most common disease and projected it would become the leading disease by 2030[6]. Unfortunately, over 30% of individuals experiencing major depressive episodes (MDEs) do not achieve remission despite multiple trials of antidepressants, and approximately 15-30% of patients with MDD are resistant to treatment[7]. Due to the absence of a universally effective treatment, additional interventions are frequently necessary. These second-step treatments may involve augmenting the initial medication with a second one or switching to a different medication to achieve better therapeutic outcomes[8]. TRD is linked to premature mortality, including suicide[7].

The genetic contribution to MDD is estimated to be around 35%, with family and twin-based studies showing higher heritability than single-nucleotide polymorphism-based estimates from genome-wide association

studies (GWAS)[9]. Both genetic and environmental factors play a role in the risk of development of major depression. Epigenetic mechanisms have been proposed to heighten the risk of depression following exposure to traumatic life events, offering a framework that integrates hereditary and environmental components[10]. "Epigenetics" refers to biological mechanisms that regulate gene expression and translation without altering the DNA sequence, including histone modifications, microRNAs, and DNA methylation (DNAm)[11]. Additionally, environmental factors such as sexual, physical, or emotional abuse during childhood are strongly linked to the risk of developing MDD[12]. No single mechanism explains all aspects of the disease. However, MDD is associated with changes in regional brain volumes, particularly the hippocampus, and functional alterations in brain circuits like the cognitive control network and the affective-salience network. The brains of individuals with depression show different structural and functional characteristics. Magnetic resonance imaging (MRI) data indicate that patients with depression exhibit grey matter loss, reduced total brain volume, altered hippocampal volume, amygdala atrophy, striatal atrophy, and reduced serotonin transporters in the amygdala[13]. One of the most frequently reported neuroimaging findings in MDD is increased connectivity and heightened activation of the amygdala[14]. The fronto-parietal cognitive control network, involved in various cognitive tasks, shows hypoconnectivity in MDD, particularly in the dorsolateral prefrontal cortex, which is implicated in goal-directed attention deficits. Numerous studies have confirmed that depression is a neurodegenerative disorder leading to atrophy in brain regions. Neurodegenerative disorders result from neuron loss, causing a decline in cognitive functioning[15]. Several studies have identified the hippocampus as a key brain region linked to depression, with hippocampal plasticity observed in patients with depression. Furthermore, disturbances in the main neurobiological stress-responsive systems, including the HPA axis and the immune system, are present in MDD[1].

Nutritional deficiencies have been noted to both trigger and worsen depression and anxiety. Additionally, research has identified a connection between inflammation and depression. Elevated levels of inflammatory markers, such as interleukin-6 (IL-6), tumor necrosis factor-alpha, C-reactive protein, and the soluble IL-2 receptor, have been found in patients with depression, suggesting a disrupted inflammatory response[16,17]. The cause of depression is also affected by nitrostative and oxidative stress. A large-scale cohort study found increased expression of genes which are involved in IL-6 signaling in the peripheral blood cells of MDD patients compared to healthy controls[18]. Patients with depression have also been exhibited with elevated cortisol levels, dysregulation of stress axis, reduced brain-derived neurotrophic factor (BDNF), and increased levels of insulin-like growth factor-1 (IGF-1) and fibroblast growth factor-1 (FGF-1)[19,20].

Neurochemistry of depression: The monoamine hypothesis

The monoamine hypothesis of major depressive disorder suggests that a decrease in specific neurotransmitters—dopamine, serotonin, and norepinephrine (NE)—in the brain leads to clinical depression. This theory is supported by the efficacy of antidepressants, which increase the levels of these neurotransmitters and subsequently reduce depressive symptoms. Numerous studies have linked depression to dysfunctions in the serotonergic, dopaminergic, and noradrenergic systems. However, recent research indicates that a deficiency in monoamines alone does not cause depression, and merely increasing neurotransmitter levels may not alleviate depressive symptoms.

The "serotonin hypothesis" of clinical depression has been proposed for over 50 years, asserting that decreased activation of the serotonin pathway contributes to the pathophysiology of depression. This hypothesis originated from the depressogenic effects of amine-depleting substances like reserpine and the antidepressant effects of medications such as monoamine oxidase inhibitors and tricyclic antidepressants. These

medications were found in animal studies to enhance the effects of serotonin and other monoamines at the synapse, discoveries that initially occurred by clinical chance[21].

Dopamine, a neurotransmitter, plays a crucial role in motivation, reward prediction, and responsiveness to everyday activities. Dysfunction in the dopamine system can lead to anhedonia, a common symptom of depression. There is substantial evidence indicating that norepinephrine (NE) is involved in depression, with recent research on neural circuits and symptoms highlighting NE's specific role in the condition[22]. NE regulates executive functioning, which includes cognition, motivation, and intellect—three essential factors for social interactions. Social dysfunction, significantly affecting the quality of life for people suffering from depression, may be one of the most impactful factors[23].

Management of depression primarily involves psychotherapy and pharmacological treatment. It is important to note that half of all completed suicides worldwide each year are associated with MDD[24]. Consequently, there is a need for newer drugs that provide rapid antidepressant effects to reduce the disease burden[25].

Currently, Selective Serotonin Reuptake Inhibitors (SSRIs) are the most commonly prescribed medications for treating depression[26]. The therapeutic effects of SSRIs are based on the monoamine hypothesis, which suggests that deficient serotonin levels cause depression. SSRIs work by inhibiting the reuptake of serotonin, thereby increasing its activity. Unlike other classes of antidepressants, SSRIs have minimal effects on other neurotransmitters, such as dopamine or norepinephrine, and they have fewer side effects compared to Tricyclic Antidepressants (TCAs) and Monoamine Oxidase Inhibitors (MAOIs) due to reduced effects on adrenergic, cholinergic, and histaminergic receptors. SSRIs inhibit the serotonin transporter (SERT) at the presynaptic axon terminal. By inhibiting SERT, more serotonin (5-hydroxytryptamine or 5HT) remains in

the synaptic cleft, allowing it to stimulate postsynaptic receptors for a longer duration[27-29].

Aside from electro-convulsive therapy (ECT), there are no widely used treatments that offer significant or rapid benefits for patients with severe depression (Martinowich et al., 2013)[30]. This presents a major clinical challenge, particularly for patients who have not fully responded to existing therapies or whose symptoms include suicidality[24]. ECT has been under-utilized due to several barriers. Healthcare professionals face obstacles such as a shortage of well-trained ECT practitioners and insufficient physical space. Patients encounter issues including stigma, negative public attitudes, and transportation difficulties. Historically, ECT has been linked to adverse cognitive effects, but recent procedural modifications, such as right unilateral administration with an ultra-brief pulse width, have mitigated these risks. Due to the cognitive side effects and other challenges associated with ECT, physician-scientists have been seeking alternative treatment modalities that provide ECT-level efficacy with more tolerable side effects and better overall acceptability[7].

Beyond monoamine hypothesis

However, the “traditional” monoamine hypothesis struggles with certain characteristics of antidepressant treatment, amongst others the week-long delay of therapeutic (but not side) effects. This is paradoxical, given that monoamine levels increase within hours after drug ingestion[31]. These (and other) drawbacks have led to a revision of the original hypothesis, in that the focus was shifted from synaptic neurotransmitter concentrations to pre- and postsynaptic receptor adaptation. Monoamine receptor sensitivity has gained prominent interest as a possible molecular pathway through which lowered synaptic transmitter levels could induce MDD. Even though deficient synaptic levels cause postsynaptic receptor upregulation, monoaminergic neurotransmission could be blunted because of receptor abnormalities[31]. Indeed, antidepressant treatment has been shown to cause postsynaptic receptor downregulation, which aligns temporally with

the therapeutic delay observed. However, many theoretical findings conflict with this approach. For example, monoaminergic treatment is effective in only 60%[32] of cases and precursor depletion is mood-neutral in healthy subjects[33]. Additionally, the effectiveness of atypical drugs, such as bupropion (which has minimal affinity for monoamine transporter proteins) and mecamylamine (a non-selective, non-competitive nicotinic acetylcholine receptor antagonist with negligible affinity for monoamine transporter proteins), cannot be reconciled with the monoamine hypotheses[34].

THE GLUTAMATE SYSTEM: A NEW TARGET

Glutamate is the most common excitatory neurotransmitter, both in cortical and subcortical areas. Chemically, glutamate classifies as an amino acid that is synthesized from glutamine via glutaminase and released from presynaptic vesicles mainly via voltage-gated Calcium channels[35]. Glutamic acid decarboxylase transforms glutamate into Gamma Aminobutyric acid (GABA), while glutamine synthetase degrades glutamate to glutamine. The effects of synaptic glutamate are terminated by glutamate transporter proteins, triggering glial reuptake and subsequent metabolization. Thus, extracellular glutamate homeostasis is tightly regulated as too little glutamate impairs synaptic plasticity while too much causes oxidative damage and excitotoxicity[36]. Postsynaptically, signals are transmitted by both ionotropic and metabotropic receptors. Beside eight different metabotropic receptors ($mGluR_1$-$mGluR_8$), there are three families of ionotropic receptors: NMDARs, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPARs) and kainate receptors[35].

Glutamate and depression

Owing to its opulent trafficking, glutamate is involved in many aspects of cognition and emotion[37]. During depressive episodes, increased concentrations of serum glutamate, blood plasma, and cerebrospinal fluid have been observed[37-39]. Imaging studies have shown elevated glutamate levels in the occipital, frontal, cingulate, and mid-cingulate

cortex, but not in the dorsolateral prefrontal cortex (DLPFC), in individuals with unipolar and bipolar depression. This is reflected by Wang *et al*. [40], who discovered that higher frontal glutamate levels distinguished between depressed and non-depressed stroke patients. Although the exact pathogenesis of excessive glutamate is not fully understood, low glial levels, particularly PFC astrocytes, have been noted throughout the brains of patients with MDD, suggesting impaired glutamate reuptake mechanisms[41-42]. Interestingly, inhibition of glutamate transporter 1 (GT1) in prefrontal areas induces anhedonia in a rat model of depression, mirroring the reduced GT1 activity seen in the medio-temporal/frontal areas and the locus coeruleus in humans with MDD[42-45].

Extensive psychopharmacological research has demonstrated that certain functional antidepressants, including fluoxetine, bupropion, curcumin, lamotrigine, riluzole, imipramine, and phenelzine, downregulate glutamatergic neurotransmission. Chronic antidepressant treatment results in an increase in hippocampal NMDAR density after withdrawal, whereas the short-term antidepressant effects of sleep deprivation may be due to NMDA receptor internalization. Post-mortem analyses of patients with depression have shown abnormalities in PFC NMDAR proteins, especially in the NR2A and NR2B subunits[46]. However, considerable controversy still surrounds associations between glutamate and mood disorders, as some studies found reduced or inconspicuous glutamate levels during depressive episodes.

For instance, Järnum *et al*. [47] failed to detect heightened glutamate levels in the cerebrospinal fluid of unipolar patients and others even found decreased glutamate/Glx (a compound index consisting of glutamate, glutamine and GABA) ratios in the anterior cingulate cortex[ACC] [48-50] and left DLPFC[51].

Scientific findings, even when keeping the stated inconsistencies in mind, hint at an involvement of excessive glutamate levels in depressive pathogenesis. Even though disease pathways of hyperglutamatergia have

not been uncovered yet, excitotoxicity-mediated neuronal atrophy is a likely candidate[52,53]. Extrapolating this to clinical medicine, there is substantial evidence indicating that antiglutamatergic drugs might be effective in alleviating depression. Crucially, reducing glutamate excitotoxicity could be the primary mechanism of action for standard antidepressant drugs, rather than merely a favorable side effect[54,55].

An increasing amount of preclinical research suggests that N-methyl-D-aspartate (NMDA) glutamate receptors play a significant role in the pathophysiology of depression and the mechanism of action of antidepressant treatments (Skolnick et al., 1996)[56]. NMDA receptor antagonists have demonstrated effectiveness in animal models of depression and in models that predict antidepressant activity in many (Layer et al 1995[57]; Meloni et al 1993 [58]; Moryl et al 1993 [59]; Papp and Moryl 1994[60] ; Przegalinski et al 1997 [61]; Trullas and Skolnick 1990 [62]) but not all (Panconi et al 1993 [63]) studies. Conversely, antidepressant administration has been shown to affect NMDA receptor function (Mjellem et al 1993 [64]) and receptor binding profiles (Paul et al 1994) [65].

Chronic, but not acute, administration of antidepressant medications consistently decreases the potency of glycine to inhibit [3H]-5,7-dichlorkynurenic acid binding to the strychnine-insensitive glycine sites. These adaptations were found in 16 of 17 tested antidepressant treatments (Paul et al 1994 [65]). A transcriptional mechanism for this phenomenon is suggested by recent evidence showing that repeated antidepressant administration regionally alters expression of mRNA that encodes multiple NMDA receptor subunits (Boyer et al 1998)[66].

Especially NMDAR antagonism has proven of interest and recent evidence argues a case for the efficacy of ketamine. Recent evidences suggests that a single sub-anesthetic dose of intravenous ketamine, glutamate-modulating agent, acutely reduces depressive symptoms in approximately 70% of MDD patients 24 hours after infusion, but these antidepressant benefits are short-lived. However, the studies reported so

far have used intravenous route to deliver ketamine. Little is known about the potential role of intramuscular ketamine in treatment of major depression[9].

Ketamine: An Emerging Antidepressant

Therapeutic options for depression primarily involve the use of antidepressants, mainly monoaminergic agents such as tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), and dual serotonin–norepinephrine reuptake inhibitors. The effectiveness of these medications relies on addressing the hypoactivity of the monoamine neurotransmitter system (mainly norepinephrine, dopamine, and serotonin), which contributes to the pathophysiology of depression. Unfortunately, current pharmacological interventions are often ineffective, as their therapeutic benefits can take weeks to appear, and only about one-third patients of depression receive adequate treatment. Individuals with TRD frequently struggle without effective pharmacological options, leading to suicidal ideation. Clinical evidence indicates that a single intravenous infusion of low-dose ketamine (0.5 mg/kg) has a rapid antidepressant effect that lasts for at least one week. Additionally, studies have shown ketamine to be an effective antidepressant for patients with TRD, particularly those experiencing suicidal ideation[67].

Ketamine, an anesthetic agent, was first developed by Calvin Stevens at Parke Davis in the 1960s as an analog of phencyclidine (CI-581). In 1964, it was approved for human trials, with 20 prisoners in Jackson prison in Michigan, USA, being the first to receive ketamine administration. Ketalar (ketamine hydrochloride) became the first Food and Drug Administration (FDA)-approved form of ketamine for individual use. Ketamine, an arylcyclohexylamine, has one chiral center and exists as two enantiomers: (R)-ketamine (or ketamine) and (S)-ketamine (or esketamine)[68].

The medical uses, side effects, and chemical structure of ketamine. It acts by blocking the N-methyl-D-aspartate receptor (NMDA). (S)-ketamine

shows a higher affinity for NMDAR than (R)-ketamine. Therefore, it was manufactured as an antidepressant. In addition, S-ketamine has higher analgesic and anesthetic effects than R-ketamine and causes fewer psychotic and other adverse effects[27].

Ketamine provides fast antidepressant effects. In a metanalysis done by Xu Y, et al [30] A large reduction in depression severity was evident within 4 hours in all but one small trial of very low-dose ketamine, and treatment effects were largest at day 1. In the 4 trials conducted with ketamine 0.5mg/kg IV. for patients with unipolar depression there was large reduction in average mood score at 24 hours remained evident, though moderately attenuated, up to day 7.

Each trial reported a significant reduction in suicidality assessed using different measures. Seven trials provided unpublished data on the suicide item component of a depression scale, 1 for HAM-D and 6 for MADRS. This systematic review of trials comparing single-dose ketamine to placebo for treatment-resistant patients in a major depressive episode confirms a significant reduction in depression severity and suicidality within 4 hours of ketamine administration [30].

Since Berman and colleagues reported the results of their initial placebo-controlled pilot trial investigating ketamine for depression treatment in 2000, numerous articles, including original studies, narrative reviews, and meta-analyses, have been published supporting ketamine's efficacy in treating depression. However, only a few of these original studies were randomized controlled trials or systematically assessed ketamine's efficacy and safety compared to a placebo or a control drug in patients with depression[69].

To date, findings from 20 randomised controlled trials have been reported, which all together include 430 participants who received ketamine. Most of these were proof of concept studies and examined the effectiveness of a single dose only, and only a few number comprehensively assessed ketamine’s safety, tolerability, and abuse potential. Very few examined the

safety (or efficacy) of repeated treatments, relative to placebo or control treatment, although repeated treatments are increasingly being used in open label studies, case studies and some clinical services[69].

Ketamine's pharmacological profile makes it a potentially useful drug for treating depression. While acute adverse effects associated with single-dose use in depression are common, they are generally transient and resolve on their own. However, high doses and repeated administration have been linked to potentially serious and possibly persistent toxic effects, observed both in patients treated for chronic pain and in recreational users of ketamine. These side effects include urological and hepatic issues, cravings or dependence, and cognitive changes[69].

EFFECT OF KETAMINE ON MDD PATIENTS

Major depression is defined by increased activation or sensitivity to noxious stimuli in limbic emotion processing and subcortical areas and insufficient activation or inadequate functioning in prefrontal cortical regions involved in emotion regulation and cognitive control processing[7].

Ketamine has been recognized as a rapid-acting antidepressant therapy in many studies. It targets the protein complex NMDAR, which is present on the surface of neurons, as mentioned previously. According to studies, inhibition of NMDAR proteins with ketamine is effective in managing the depressive-like behaviour more quickly and than traditional antidepressant medications[70].

Miller, Yang, and colleagues developed a rodent line (named 2BCtx) that lacks the GluN2B subunit in excitatory neurons to investigate the effects of ketamine on NMDAR proteins. They conducted two tests to evaluate the baseline levels of depressive-like symptoms in 2BCtx mice: the forced swim test and the tail suspension test. In these tests, a rodent with depressive-like symptoms spends less time moving than a wild-type rodent, indicating behavioral despair, a key characteristic of depression in humans. The 2BCtx rodents spent more time moving than the wild-type

rodents in both tests, suggesting they exhibit fewer depressive-like symptoms[71].

In patients with depression, new research links specific variations in a network of subcortical, prefrontal, and limbic brain areas. It is found that sub-anaesthetic dose of ketamine partially inhibits NMDA receptors, specifically GluN2B subunits and its therapeutic response is mediated by AMPA-type glutamate receptors[72]. According to one theory, ketamine enhances AMPA and NMDA receptor function and density by directly blocking NMDA receptors and indirectly increasing AMPAR function and density[71,73] as shown in (Figure 1), which activates downstream synaptogenic signaling pathways, restoring synaptic connectivity and strength in the prefrontal cortex and the hippocampus [73].

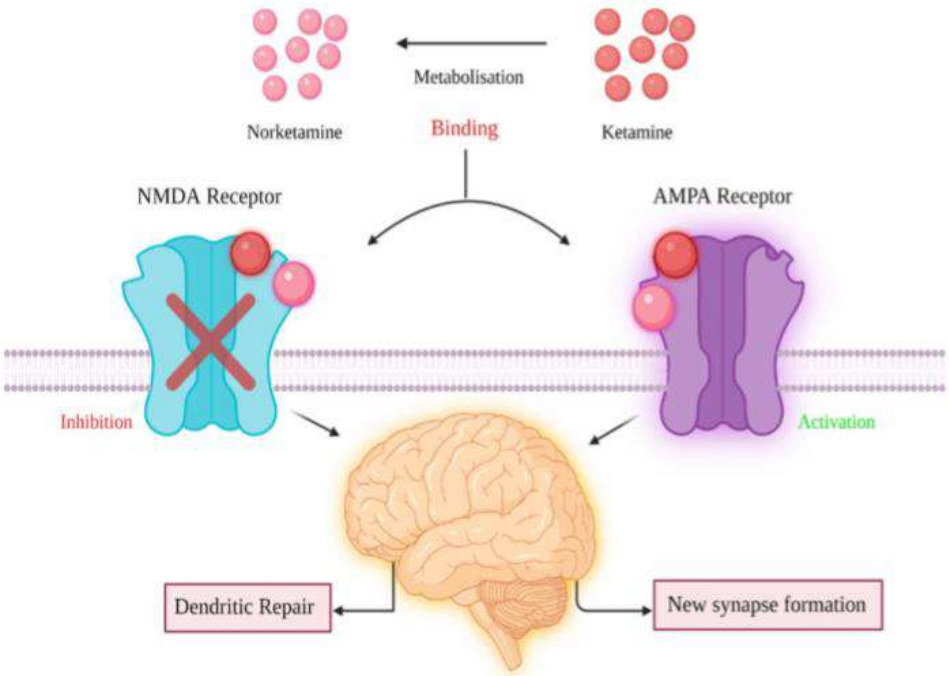


FIGURE 1: Effect of ketamine metabolites acting on N-methyl D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl4-isoxazolepropionic acid (AMPA) receptors. The binding of ketamine or nor-ketamine will inhibit the activity of the NMDA receptor. In contrast, if ketamine binds to the AMPA receptor, it will be activated and will initiate downstream signaling

activities; both by inhibiting the NMDA receptor and activating the AMPA receptor which promote the formation of new synapses and the repair of neuronal dendrites. This process helps to reverse the negative effects of depression or stress associated with posttraumatic stress disorder in patients.

Amino acid, neuropeptide, monoamine, and neuroendocrine transmitter systems influence behavioural changes by influencing the connection of neurons inside our brain[71]. Ketamine acts by bringing these mood-regulating mechanisms back into balance. According to positron emission tomography, ketamine increases neuronal activation in prefrontal cortex (PFC)[74]. It was also discovered to activate the mTOR pathway quickly, which lead to an increase in synaptic signaling proteins and improved function and a number of new spine synapses in mouse PFCs[70]. These findings support the notion that the antidepressant effects of NMDA receptor antagonists are linked to increase in neuroplasticity and neurotrophic-related factors, as well as broader neurotrophic theories of depression[75]. Although it is clear that ketamine exerts antidepressant effects by altering emotion regulation and processing systems in the brain, the exact nature of these changes is still unknown.

Various Routes of Ketamine

1. Intravenous Ketamine
2. Intranasal Ketamine
3. Oral Ketamine
4. Intramuscular Ketamine
5. Subcutaneous Ketamine

Intravenous Ketamine: In this the drug is injected into the vein, travels through the bloodstream, and reaches its CNS targets without the first-pass effect. IV ketamine, by definition, has 100% bioavailability. When used for sedation or analgesia, the starting dose by this route is 0.25-1 mg/kg for adults and 0.25-2 mg/kg for children. Anesthetic doses are typically higher. Depressive symptoms respond to as low as 0.1-0.75

mg/kg, given as a 40-45-minute infusion. Two treatments every week are needed for longer-lasting relief. Some patients achieve remission after 6 sessions[76].

Intranasal Ketamine: Its analgesic efficacy is similar to that of IV morphine. Direct intravascular infusion produces rapid plasma peaking, poses the largest risk for side effects, but also for rapid titration and discontinuation. Intranasal ketamine takes advantage of the rich vascularity inside the nose and its unimpeded access to the blood-brain barrier. Bioavailability is about 45-50%, though it can be much higher if Ketamine does not spread into the pharynx or reach the lips[77].

Subanesthetic doses are within the 0.25-4 mg/kg range and may be given for pain management and non-anesthetic applications. Analgesic effects manifest 5-15 minutes after intake and last up to 3 hours. Intranasal racemic ketamine may be used as an analgesic or anesthetic agent. For depression, the esketamine nasal spray, Spravato, is the one with FDA approval. Its dosing schedule is 56-84 mg twice per week for four weeks, then tapered afterward. Racemic ketamine given intranasally at 50 mg has also shown promise in the treatment of depression[9].

Oral Ketamine: For analgesia and sedation, the oral ketamine dose is 3-15 mg/kg in children and up to 500 mg in adults. Antidepressant dosing is generally lower and has less abuse potential. An oral dose of 1 mg/kg three times a week was found to be an effective adjunct in TRD, though it still doesn’t beat IV ketamine treatment. The onset of analgesia for regular oral preparations is 30 minutes, with a duration of about 4-6 hours. Meanwhile, the antidepressant effect of extended-release oral ketamine, though delayed, is comparable to that of the subcutaneous drug[78,79].

Intramuscular Ketamine: IM ketamine injection has a 93% bioavailability, 5-minute analgesic onset and 0.5-2-hour effect duration. The starting dose for pain management is 4-5 mg/kg. For treating depression IM dosing has been studied much less and therefore is not utilized as often clinically. However, a small, open-label, randomized trial showed that the

intramuscular injection of 0.25-0.5 mg/kg ketamine was as effective and safe as 0.5 mg/kg intravenous infusion in treating depression (Chilukuri et al., 2014)[80].

Subcutaneous Ketamine: The subcutaneous route uses the hypodermal capillaries for drug absorption. Like its intramuscular version, SC ketamine also has nearly complete bioavailability, although the onset of analgesia may take up to 30 minutes. Effect duration is also similar to that of IM ketamine. The effective dose of SC ketamine for pain management has not been established. However, subcutaneous infusions ranging from 0.1 to 1.2 mg/kg/hour have been utilized for chronic pain[81].

KETAMINE AND NEUROTOXICITY

Ketamine exerts psychedelic and psychotropic effects on the central nervous system. Psychedelic side effects depend on the amount of dose infused during the treatment of chronic pain. The perception of reality is affected, causing panic attacks, increased awareness of sound and space, auditory hallucinations, visual hallucinations, paranoid ideas, and inability to control thoughts. Moreover, some patients experience intense euphoria, dizziness, vertigo, nausea, blurred vision, nystagmus, vivid dreams, memory deficits, dysphasia, and impaired motor function. An assessment of cognitive and memory functioning during a short duration of treatment with ketamine revealed impairments in working memory and declines in data encoding into episodic memory. Moreover, in contrast to different amnestic drugs, it induces semantic memory impairment[82].

Psychedelic effects of ketamine show psychological dependence long-term abuse[83]. Recurrent ketamine abusers show more damage to the brain by causing neurotoxicity. Studies in the developing rodent brain reported that NMDAR antagonists induce neuro-degeneration through apoptosis, and enhancement of excitatory neuronal activity in the brain causes neuronal injury[84]. Liao et al. observed the toxicity of ketamine in an adult brain in two studies. They reported that brain volume in ketamine abusers decreases, that is, degeneration in white matter was observed in

the temporo-parietal cortex and reduced gray and white matter volume was observed in the bilateral frontal cortex[85].

Numerous studies revealed that patients with a history of substance abuse should avoid ketamine treatment. Ketamine has indirect stimulatory and direct inotropic effects on the cardiovascular system. It activates the sympathetic nervous system, leading to stimulation by inhibiting norepinephrine reuptake, vagal nerve inhibition, and catecholamine release at peripheral nerves. Both high and low doses of ketamine can cause myocardial depression, which is characterized by increased myocardial oxygen consumption and cardiac output, as well as tachycardia and pulmonary hypertension[86]. Some reports also show that ketamine treatment leads to increased liver enzyme profile; continuous low-dose and high-dose ketamine infusions led to a 10% elevated liver enzyme profile and it took 3 months for this to return to normal. Although the mechanism by which ketamine induces injury in the liver is not entirely understood, some plausible factors include an increase in lipid peroxidation along with the production of free radicals, a decrease in hepatic oxygen, and allergic hepatitis[87]. These findings demonstrate the adverse effects of ketamine when used in uncontrolled settings. While on ketamine treatment, patients should be continuously monitored and treatment must be discontinued if any side effects are observed. Additional side effects of ketamine have been observed in recreational ketamine users, including urinary abnormalities, chronic schizotypal behavior, and memory problems [88]. An increase in caspase-3 and Fluoro-Jade C-positive neuronal cells was observed in the frontal cortex of rats administered six injections of 20mg/kg ketamine. The typical nuclear condensation and fragmentation observed under electron microscopy indicated heightened apoptotic features. Other parts of the brain also showed increased cell death, which can lead to neurodegeneration[89].

Notably, safety issues have been reported for other groups administerd ketamine, such as individuals with chronic pain and recreational users.

Various reviews, including those from the WHO[90], have identified urinary tract symptoms as a notable side effect of ketamine and noted potential harms like liver toxicity, cognitive changes, and dependence[91]. In 2012, Morgan and Curran[92], representing the Independent Scientific Committee on Drugs, found that daily use of ketamine is linked to ulcerative cystitis and neurocognitive deficits in working and episodic memory. Additionally, many frequent users have expressed concerns about addiction. Despite the 15 years since Berman and colleagues' report, there is still a notable knowledge gap regarding the long-term efficacy of ketamine in treating depression, potential long-term safety concerns, and the lack of approved guidelines for its use[93-96].

Patients suffering from MDD currently have limited treatment options, deficient in terms of both the time scale over which these medications act and the fact that a significant number of ill individuals do not respond to the currently available pharmacopeia. Some studies support the rapid actions of ketamine (IV and IM) and SSRIs when given in combination in MDD. Therefore, this study investigated the comparative efficacy intravenous versus intramuscular ketamine on patients suffering from MDD who are already taking SSRIs. It will provide insights into the rapid antidepressant effectiveness of ketamine when used alongside standard treatment.

AIMS AND OBJECTIVES

1. To compare the therapeutic efficacy of ketamine given by intravenous route versus intramuscular route in patients of Major Depressive Disorder(MDD).

Domino EF et al [97] in 1965, first studied ketamine, a phencyclidine derivative then known as CI-581, in 20 volunteers from a prison population. They established its efficacy as a dissociative anesthesia agent with a rapid onset and limited duration of action.

Krystal JH et al[98] studied behavioral, cognitive, neuroendocrine, and physiological effects of sub-anesthetic doses of ketamine hydrochloride in nine healthy human subjects. Amongst other findings, note was also made of dose-dependent alteration of mood states following ketamine administration. Subjects experienced a high, a euphoric feeling that made for a pleasant experience. They also found that Ketamine at low doses also have anxiolytic effect.

Trullas and Skolnick[62] findings indicate that the NMDA receptors may be involved in the behavioral deficits induced by inescapable stress, and that substances capable of reducing neurotransmission at the NMDA receptors may represent a new class of antidepressants. Further studies demonstrated anti-depressant like actions of other NMDA antagonist agents i.e. CGP 397849 and CCP 39551 memantine and eliprodil, an NMDA antagonist acting through polyamine coupled sites.

A review conducted by **Skolnick et al**[56] in 1996 concluded three consistent findings that clearly demonstrated the role of NMDA receptors in depression. Chronic treatment with functional NMDA antagonists led to down-regulation of cortical beta adreno-receptors. Cortical beta adreno-receptor down-regulation is a consistent finding with antidepressant use. Chronic anti-depressant treatment produced adaptive changes in radio-ligand binding to NMDA receptors. Functional NMDA receptor antagonists demonstrated anti-depressant like actions in preclinical animal studies.

ROLE OF KETAMINE IN DEPRESSION-

Berman et al.,[99] in 2000 conducted a placebo controlled, double blinded trial to know the treatment effects of a single dose of ketamine versus placebo in 7 patients with depression as per DSM-IV. Patients underwent

two treatment days separated by at least 1 week. A saline solution alone or containing ketamine hydrochloride (total dose of 0.5 mg/kg) was infused over 40 min. Four participants were randomly assigned to receive ketamine (0.5 mg/kg) prior to placebo infusion. Ratings included the HDRS;(baseline as well as 80 min, 230 min, 24 hours, 48 hours, and 72 hours after starting infusion), BDI; (baseline as well as 10, 40, and 110 min after infusion), Visual Analog Scales score for intoxication “high” (VAS-high; baseline as well as 10, 40, 80, and 110 min after infusion). It was observed that intravenous ketamine produced significant greater reduction on HDRS score, thus suggesting its potential role in NMDA receptor modulation in depression.

Zarate et al.,[81] in 2006 conducted a randomized, placebo-controlled, double blind crossover study on 18 subjects with TRD to determine the rapid anti-depressant effect of ketamine. Following a 2-week drug-free period, 18 subjects with MDD (DSM-IV criteria) received intravenous infusions of saline solution and 0.5 mg/kg of ketamine hydrochloride, 1 week apart. Patients were randomly assigned to the order in which they received the 2 infusions via a random-numbers chart. The infusions were administered over 40 minutes via an infusion pump. Subjects were rated 60 minutes prior to the infusion and at 40, 80, 110, and 230 minutes, as well as 1, 2, 3, and 7 days, after the infusion. Rating scales included the 21-items HDRS, which was the primary outcome measure, and the secondary outcome measure was Beck Depression Inventory (BDI). The study indicated significant improvement for ketamine over placebo at 110 minutes through 7 days. Of the 17 subjects treated with ketamine, 71% met response and 29% met remission criteria the day following ketamine infusion. Thirty-five percent of subjects maintained response for at least 1 week.

Paul et al.[100] (2009) published case report examining the effects of racemic ketamine versus S-ketamine in patients with TRD. The participants were two patients with TRD, each treated with either racemic

ketamine or S-ketamine. Each patient received a single infusion of racemic ketamine (0.5 mg/kg) or S-ketamine (0.25 mg/kg) over 40 minutes. One patient showed a marked reduction in depressive symptoms within hours of receiving racemic ketamine, with effects lasting up to one week. The second patient experienced notable improvement in depressive symptoms with S-ketamine, though the duration of effect was shorter compared to racemic ketamine. Both formulations were well-tolerated, with adverse effects including mild dissociative symptoms and transient increase in blood pressure, similar to those observed with racemic ketamine. The case report suggests that both racemic ketamine and S-ketamine can provide rapid antidepressant effects in TRD, with racemic ketamine potentially offering longer-lasting benefits. However, further research with larger sample sizes is needed to confirm these findings.

Price B et al [101] in 2009 investigated the effects of intravenous ketamine on explicit and implicit measures of suicidality in TRD. Twenty-four hours after a single infusion, MADRS-SI scores were reduced on average by 2.08 points, with 81% of patients receiving a rating of 0 or 1 post-infusion. Repeated-dose ketamine sustained reductions in MADRS-SI scores for 12 days. Implicit suicidal associations were also reduced following ketamine, suggesting a rapid beneficial effect on suicidal cognition.

DiazGranados, N et al[102] in 2010 conducted study included 33 participants aged 18-65 diagnosed with treatment-resistant MDD. They received a single open-label infusion of ketamine (0.5 mg/kg) and rated at baseline, 40, 80, 120, and 230 minutes post-infusion with the SSI, the MADRS, HDRS, and the BDI. Suicidal ideation scores decreased significantly on the SSI as well as on the suicide subscales of other rating instruments within 40 minutes; these decreases remained significant through the first four hours post-infusion ($p<.001$). Ten subjects (30%) had a SSI score 4 at baseline, and all dropped below a score of 4 (nine by 40 minutes and one by 80 minutes). For those starting below a score of 4 on the SSI, only one reached a score of 4. Depression, anxiety, and

hopelessness were significantly improved at all time points (p<.001). Suicidal ideation in the context of MDD improved within 40 minutes of a ketamine infusion and remained improved for up to four hours post-infusion. Future studies with ketamine in suicidal ideation are warranted due to its potential impact on public health.

Aan Het Rot et al [103] in 2010 examined the efficacy and safety of repeated-dose intravenous (IV) ketamine for the treatment of TRD. They found that Ketamine elicited minimal positive psychotic symptoms. Three patients experienced significant but transient dissociative symptoms. Side effects during and after each ketamine infusion were generally mild. The response criterion was met by nine patients after the first infusion as well as after the sixth infusion. The mean (SD) reduction in MADRS scores after the sixth infusion was 85% (12%). Post-ketamine, eight of nine patients relapsed, on average, 19 days after the sixth infusion (range 6 days– 45 days). One patient remained antidepressant-free with minimal depressive symptoms for 3 months.

Zarate Jr et al.[104] (2012) in their study, researchers examined the effectiveness of ketamine as an add-on treatment for patients with bipolar depression through a RCT. They included adults with bipolar depression who had not shown response adequately to at least one antidepressant. Participants received a single intravenous infusion of ketamine (0.5 mg/kg) or a placebo, administered over 40 minutes. The ketamine group showed marked decrease in MADRS scores compared to the placebo group as early as 40 minutes post-infusion, with these effects persisting for up to three days. Ketamine was generally well-tolerated, with the most common side effects being dissociative symptoms and transient increases in blood pressure, both of which resolved shortly after the infusion.

James W. Murrough et al.[105] in 2013 conducted a two-site RCT to evaluate the efficacy of ketamine as an antidepressant in TRD. This parallel-arm trial compared a single infusion of ketamine to an active placebo control, the anesthetic midazolam. Patients with TRD

experiencing a major depressive episode were randomly assigned under double-blind conditions to receive a single infusion of either ketamine or midazolam in a 2:1 ratio (N=73). The primary outcome was the change in depression severity 24 hours after drug administration, measured by the MADRS. The results indicated that the ketamine group showed significant improvement in MADRS scores compared to the midazolam group 24 hours post-treatment. After adjusting for baseline scores and site, the MADRS score was 7.95 points lower in the ketamine group than in the midazolam group (95% confidence interval [CI], 3.20 to 12.71). The likelihood of response at 24 hours was higher with ketamine than with midazolam (odds ratio, 2.18; 95% CI, 1.21 to 4.14), with response rates of 64% and 28%, respectively. The authors concluded that ketamine demonstrated rapid effects as an antidepressant in an optimized study design, supporting NMDA receptor modulation as a novel mechanism for accelerated improvement in severe and chronic forms of depression. However, more information on response durability and safety is needed before clinical implementation.

H.W.W. Hasselmann et al[67] in 2013 reviewed Ketamine as Antidepressant w.r.t. current state and future perspectives. Initial research argues the case for excessive glutamate levels, suggesting that antiglutamatergic drugs might be useful in treating MDD. Ketamine is a non-selective, high-affinity N-methyl-D-aspartate receptor (NMDAR) antagonist most commonly used in pediatric and animal surgery. In the past, ketamine has gained popularity because of its ability to rapidly elevate mood, even in treatment-resistant and bipolar depression. However, there are still many obstacles before widespread clinical approval of ketamine treatment could become reality. In this review, ketamine’s powerful antidepressant effects are discussed and further research necessary for therapeutic application is outlined. NMDAR antagonists provide an entirely new way of treating the manifold appearances of depression that should not be left unused.

Sos, P et al. [106] (2013) in a double-blind, cross-over, placebo-controlled, two weeks clinical trial studied the effects of ketamine (0.54 mg/kg within 30 min) in a group of 27 hospitalized depressive patients. Higher intensity of psychotomimetic symptoms, measured using BPRS, during ketamine administration correlated with alleviation in mood ratings dur- ing the following week with maximum on day seven. Ketamine was superior to placebo in all visits (day 1, 4, and 7) assessed by MADRS. There was no significant correlation between ketamine and nor-ketamine plasma levels and MADRS score change at any study time point. The substantial relationship between ketamine's antidepressant and psychotomimetic effects was found. This relationship could be mediated by the initial steps of ketamine's action, trough NMDA receptors, shared by both ketamine's clinical effects.

Scott A. Irwin et al.[79] in 2013, investigated the effects of oral ketamine given daily on depression and anxiety in patients receiving hospice care. Marked improvement in depressive symptoms was observed by day 14 (mean D=3.5, d=1.14, 95% CI=1.09–5.9, p=0.01), and significant improvement in anxiety was noted by day 3 (mean D=2.4, d=0.67, 95% CI=1.0–3.7, p=0.004). These improvements remained significant through day 28 for both depression (p=0.001) and anxiety (p<0.001). Side effects were rare, with the most common being diarrhea, trouble sleeping, and difficulty sitting still. The authors concluded that daily oral ketamine led to a significant antidepressant and anxiolytic response with minimal adverse events. The response rate for depression was similar to that found with IV ketamine, although the time to response was longer. These results suggest the potential efficacy of oral ketamine for depression and anxiety symptoms, highlighting the need for further investigation through RCT to establish the efficacy and safety of oral ketamine for treating depression and anxiety in hospice care patients or other populations.

Harihar Chilukuri et al.[80] in 2014, analyzed the acute antidepressant effects of intramuscular versus intravenous ketamine. This randomized,

open-label, parallel-group study was conducted in a tertiary care teaching hospital with a sample of 27 subjects with major depression, divided randomly into three groups of nine subjects each. Each group received ketamine at a dose of 0.5 mg/kg as an IV infusion, 0.5 mg/kg IM, or 0.25 mg/kg IM. Depression was assessed using the HAM-D before the injection, two hours later, the next day, and three days later. The results showed that mean age of the participants was 36.81 years (SD 11.815). Two hours post-injection, HAM-D scores decreased by 58.86%, 60.29%, and 57.36% in each group, respectively, with improvement sustained for the next three days. Adverse effects were rare, mild, and transient, lasting less than an hour. The authors concluded that intramuscular ketamine at a dose of 0.25 mg/kg is as effective and safe as 0.5 mg/kg given either IM or IV, significantly reducing depressive symptoms within a few hours and maintaining this effect for three days.

Hu et al. in 2104[107] conducted a randomized, placebo-controlled study to evaluate the safety and efficacy of a single IV dose of ketamine as an augmentation strategy for newly initiated escitalopram treatment in patients with severe depression. The study included 30 outpatients with severe MDD, who were randomized to receive either escitalopram 10 mg/day combined with a single IV dose of ketamine (0.5 mg/kg) or escitalopram 10 mg/day combined with a placebo (0.9% saline). After four weeks, a higher proportion of patients treated with escitalopram and ketamine responded (92.3% vs. 57.1%, $p = 0.04$) and achieved remission (76.9% vs. 14.3%, $p = 0.001$), with a significantly shorter time to response compared to those treated with escitalopram and placebo. The escitalopram plus ketamine group had significantly lower MADRS scores from 2 hours to 2 weeks (peak effect at 3 days to 2 weeks; effect size (ES) = 1.08–1.18), QIDS-SR scores from 2 hours to 2 weeks (maximum ES = 1.27), and QIDS-SR suicidality scores from 2 to 72 hours (maximum ES = 2.24). Mild and transient side effects, such as dissociative symptoms, nightmares, restlessness, dizziness, nausea, and headache, were

reported and resolved within 24 hours post-infusion. There were no marked differences in psychotic or dissociative symptoms between the two groups.

Ballard et al. in 2014 [108] in their study examined the effects of ketamine on suicidal ideation in patients with TRD. The findings revealed significant reductions in suicidal ideation within 40 minutes of a single ketamine infusion, with these effects lasting up to one week. These reductions were strongly associated with decreases in both depression and anxiety symptoms, indicating ketamine's potential as a rapid-acting treatment for acute suicidality in patients with TRD. The study included 20 patients with treatment-resistant MDD, who underwent FDG-PET imaging to measure cerebral glucose metabolism before and after a single ketamine infusion. The objective was to pinpoint specific brain regions linked to suicidal ideation and observe the changes in these regions following ketamine treatment. Nineteen medication-free patients with treatment-resistant MDD underwent PET imaging at baseline and 230 minutes after an open-label ketamine infusion (0.5 mg/kg for 40 minutes). The study found a significant correlation between baseline suicidal ideation and regional cerebral glucose metabolism in the infralimbic cortex ($r = .59$, $P = .007$), but not overall mood scores ($r = -.07$, $P = .79$). Reductions in suicidal ideation following ketamine infusion were correlated with decreased regional cerebral glucose metabolism in the infralimbic cortex ($r = .54$, $P = .02$). Metabolism in other areas of interest was not correlated with suicidal ideation or depression. The results indicated a marked correlation between baseline suicidal ideation and increased glucose metabolism in the infralimbic cortex (Brodmann area 25). Furthermore, reductions in suicidal ideation post-ketamine were associated with decreased metabolism in this brain region.

Singh JB et al.[109] in 2016 evaluate the efficacy of two dosing regimens—twice a week and three times a week—of intravenous ketamine (0.5 mg/kg) compared with placebo in sustaining initial antidepressant efficacy

in TRD patients.The mean change in MADRS score at day 15 was significantly greater for ketamine compared to placebo in both dosing regimens:Twice-weekly: -18.4 (SD=12.0) for ketamine vs. -5.7 (SD=10.2) for placebo and Thrice-weekly: -17.7 (SD=7.3) for ketamine vs. -3.1 (SD=5.7) for placebo. A higher proportion of patients in the ketamine groups showed a rapid onset of clinical response within the first week, maintained through day 15:Twice-weekly: 38.9% for ketamine vs. 6.3% for placebo and Thrice-weekly: 23.5% for ketamine vs. 0% for placebo. A higher proportion of patients in the ketamine groups showed a rapid onset of clinical response within the first week, maintained through day 15:Twice-weekly: 38.9% for ketamine vs. 6.3% for placebo and Thrice-weekly: 23.5% for ketamine vs. 0% for placebo. Study demonstrated that both twice-weekly and thrice-weekly administration of intravenous ketamine at 0.5 mg/kg maintained antidepressant efficacy over 15 days in patients with TRD. The study highlighted ketamine's potential as a rapid-acting antidepressant, offering significant improvements in symptoms of depression and onset of response compared to placebo.

Kishimoto et al. [76] in 2016 done a meta-analysis of ketamine and NMDA receptor antagonists to evaluate the efficacy, safety, and time trajectories of single-dose ketamine and other non-ketamine NMDA receptor antagonists in unipolar and bipolar depression. The analysis found that ketamine demonstrated rapid antidepressant effects within hours, with significant symptom reduction lasting up to one week. In contrast, non-ketamine NMDA antagonists showed less consistent results. Ketamine was generally well-tolerated, with common adverse effects including transient dissociation and elevated blood pressure. The rapid onset and short duration of ketamine's effects underscore the need for strategies to extend its antidepressant benefits.

Ying Xu et al.[30] in 2016 conducted, a systematic review and meta-analysis to evaluate the effects of low-dose and very low-dose ketamine in patients with depression. The review encompassed nine trials involving

two hundred one patients (52% female, mean age 46 years). Six trials examined low-dose ketamine (0.5 mg/kg IV), while three trials investigated very low-dose ketamine (one trial used a 50 mg intranasal spray, another tested 0.1–0.4 mg/kg IV, and the third assessed 0.1–0.5 mg/kg IV, IM, or SC). By day 3, the significant decrease in depression severity scores was less significant in the very low-dose trials (P homogeneity <.05) and among patients of bipolar disorder. Excluding the second period of crossover trials, response rates at day 7 were higher with ketamine (P=.001), as were remission rates (P=.02). The absolute benefits were notable, with day 7 remission rates of 24% compared to 6% (P=.02). Seven trials provided unpublished data on suicidality item scores, which were reduced on days 1 and 3 (both P<.01) but not on day 7. The authors concluded that low-dose ketamine appears more effective than very low-dose ketamine.

Andrew J. Hvizdos et al.[110] in 2016, examined the use of ketamine for the acute management of depression. Ketamine, an antagonist at the N-methyl-D-aspartate (NMDA) receptor, produces rapid antidepressant effects at a low dose of 0.5 mg/kg administered intravenously over 40 minutes. Response rates range from 25% to 100%, and remission rates vary from 8.3% to 89%. The duration of response spans from less than one week to more than three months. Significant hemodynamic and psychiatric adverse effects are associated with ketamine use, and its potential for abuse has raised concerns.

Schwartz, Murrough, and Iosifescu[111]. in 2017, conducted a randomized, double-blind, placebo-controlled trial involving adults diagnosed with TRD who had not responded to two prior antidepressant treatments. Participants received a single infusion of IV ketamine (0.5 mg/kg) or a placebo (saline) over 40 minutes. Significant reductions in MADRS scores were observed within 24 hours of ketamine infusion compared to the placebo. The rapid onset of antidepressant effects highlighted ketamine's potential for immediate relief in TRD patients. A

substantial proportion of participants achieved a clinical response (≥50% reduction in MADRS scores) and remission (MADRS score ≤10) at 24 hours post-infusion. The study identified other clinical predictors of efficacy, including increased body mass index (BMI), family history of alcohol use disorder, and anxious depression. Additionally, a correlation was found between the extent of dissociative symptoms and the antidepressant response, with higher CADSS scores associated with greater reductions in MADRS scores, suggesting a potential link between dissociation and therapeutic outcomes.

Li et al.[112] 2017 in their meta-analysis on Ketamine in Electroconvulsive Therapy (ECT), investigated the effects of adding ketamine anesthesia to ECT for patients with depression. They found that combining ketamine with ECT show improvement in depressive symptoms compared to ECT alone. The combination was well-tolerated, with side effects similar to those of either ketamine or ECT when used independently.

Wilkinson et al.[113] in 2017, conducted a systematic review and individual participant data meta-analysis to examine the effects of a single IV dose of ketamine on suicidal ideation. They performed a comprehensive search of MEDLINE for terms related to ketamine, NMDA receptor antagonists, rapid antidepressants, and suicide, focusing on studies published between January 2000 and November 2016. The analysis included only comparison intervention studies using saline or midazolam as control treatments. Data from 167 patients with baseline suicidal ideation from 10 of the 11 identified studies were included. The results showed that ketamine significantly reduced suicidal ideation within one day of administration, at all post-dosing time points. Marked decrease in suicidal ideation were observed on the MADRS and HAM-D, with benefits lasting from day 1 to day 7 post-infusion. Significant reductions were also noted on the QIDS-SR, but not the BDI. The benefits of ketamine compared to control treatments were significant at all time points except day 7. Ketamine's effect on suicidal ideation remained significant even after

adjusting for changes in the severity of depressive symptoms, suggesting that its antisuicidal effects are partially independent of its antidepressant effects. Among patients who achieved resolution of suicidal ideation within 24 hours post-infusion, the effects persisted for up to one week in a significant proportion of patients. Ketamine was generally well-tolerated, with manageable side effects including transient dissociative symptoms and increases in blood pressure.

Chittaranjan Andrade et al. [77] in 2017 conducted a study on ketamine for depression- clinical summary of issues related to efficacy, adverse effects, and mechanism of action. Ketamine is an anesthetic drug that is also used for off-label indications such as the mediation of analgesia and sedation in various settings. It is additionally recognized as an agent with antidepressant potential. For depression, it is most commonly administered as a slow intravenous infusion in subanesthetic doses (usually 0.5 mg/kg). As an antidepressant, is strikingly different from conventional antidepressant drugs in that it brings about rapid and marked attenuation in symptoms of depression even in patients with refractory depression. The benefits are observed within hours of administration, peak after about a day, and are lost 3–12 days later. Patients who do not benefit after the initial dose may benefit with serial dosing or at higher doses. Benefits can be maintained for weeks to months by the continuation of ketamine sessions at 2- to 4-day intervals. Adverse effects include dissociative and psychotomimetic changes that are almost always mild and transient, if present; transient elevation of heart rate and blood pressure often occur. These changes are usually well tolerated and are very seldom responsible for treatment discontinuation. While ketamine is known as an N-methyl-D-aspartate receptor antagonist and its various biological effects are well-documented, the specific actions responsible for its antidepressant response are not yet fully understood. Although extensive data on ketamine are currently lacking, the drug shows promise in treating depression, particularly TRD.

Tung-Ping Su et al[114] in 2017 conducted a study on dose-related effects of ketamine as an adjunct in patients with TRD. Authors conducted a double-blind, randomized, parallel-group, placebo-controlled trial of a single ketamine infusion (saline, 0.2 mg/kg, 0.5 mg/kg). Patients (N= 71; BDNF genotype: Val/Val (N=12, 17%), Val/Met (N=40, 56.3%), and Met/Met (N= 19, 26.8%)) received mood ratings before infusion, after infusion, and for the subsequent 14 days. Plasma ketamine levels and BDNF genotypes were assessed. This study found a significant dose-related ketamine effect on scores on the HAMD. The responder analysis (450% reduction from baseline HAMD on at least 2 days between days 2 and 5) also revealed a significant dose-related effect (saline: 12.5%, 0.2 mg/kg: 39.1%; 0.5 mg/kg: 45.8%). This demonstrate the dose-related efficacy of R/S-ketamine for TRD and the first to characterize ketamine effects in a genotyped Chinese population in which most (83%) patients possessed at least one copy of the lower functioning Met allele of the BDNF gene.

Rybakowski et al.[115] in 2017 in their study focused on the rapid improvement in depression scores with ketamine augmentation in treatment-resistant bipolar depression. Significant reductions in depression scores were observed within hours of ketamine administration. The antidepressant effects were sustained for several days post-administration.

Brooke Short et al.[69] in 2017, conducted a systematic review to examine the side effects associated with ketamine use in depression treatment. The review identified 288 articles from databases including MEDLINE, PubMed, PsycINFO, and Cochrane, with 60 of these articles meeting the inclusion criteria. The analysis revealed that following acute dosing, side effects were more frequently reported in patients receiving ketamine compared to those receiving a placebo. These side effects included psychiatric, psychotomimetic, cardiovascular, and neurological effects, among others. This is despite such side effects being documented in other

groups exposed to ketamine, such as individuals with chronic pain and recreational users. The authors of the review recommended conducting large-scale clinical trials involving multiple doses of ketamine and long-term follow-up to thoroughly evaluate the safety of regular long-term ketamine use.

Fava M et al. [116] [2018] in a double-blind, placebo-controlled, dose-ranging trial involved 99 adults with TRD (TRD), who were randomly selected to receive either ketamine at doses of 0.1, 0.2, 0.5, or 1.0 mg/kg, or midazolam (placebo). The treatments were administered over a 40-minute period. The study found that the 0.5 mg/kg and 1.0 mg/kg doses of ketamine produced significant antidepressant effects compared to the active placebo, with the most notable effects observed on day 1 post-infusion and sustained improvements in some participants lasting up to day 7. Ketamine was generally well-tolerated, with the most commonly reported side effects being transient dissociative symptoms, which resolved within hours after the infusion. No severe adverse events were reported during the trial. Additionally, a correlation was identified between dissociative symptoms, as measured by the CADSS, and the antidepressant effects of ketamine, suggesting that dissociation can contribute to its therapeutic mechanism.

Arabzadeh S, et al. [117] in 2018, conducted a study on a double-blind controlled trial to investigate whether oral administration of ketamine accelerates the response to treatment in major depressive disorder. The authors employed a double-blind controlled trial to examine the therapeutic effect of ketamine when combined with the conventional administration of sertraline. Total of 81 patients participated and were scored using the HDRS at baseline and 2, 4, and 6 weeks after the trial began. Results showed a significant effect for time × treatment interaction on the HDRS scores, with significant differences at all post-treatment time points. Early improvement was significantly greater in the ketamine group (85.4%) compared to the placebo group (42.5%). No side effects were

observed for ketamine administration. A limitation of the study was the follow-up period, which was limited to 6 weeks post-initiation of treatment, preventing the assessment of potential long-term adverse effects of oral ketamine and the sustainability of its benefits. The authors concluded that their results suggest oral ketamine may be a suitable adjunct to sertraline in alleviating depressive symptoms.

Zanos, P. And Gould, T.[118] in 2018 studied mechanisms of ketamine action as an antidepressant. Understanding the mechanisms underpinning ketamine's antidepressant actions not only provides invaluable information on the neurobiology of major depression but it also drives the identification of novel therapeutic targets for the development of the next generation rapid-acting antidepressants, which will be effective and lack undesirable side effects. NMDAR inhibition produces serious side effects, even at low, sub-anesthetic and antidepressant-relevant doses, which makes long-term use of agents fully blocking this receptor impractical for the treatment of depression. The NMDAR inhibition independent hypothesis of the antidepressant actions of ketamine reviewed here provides a framework to guide future studies on the identification of novel targets for the long-term treatment of depression lacking such side effects.

In a systematic review of multiple clinical trials done by **Park et al.**[119], Ketamine produce a rapid reduction in depressive symptoms, often within hours of administration. There was a marked reduction in suicidal thoughts shortly after ketamine administration, especially within the first 24 hours post-infusion, and this effect was sustained for up to one week in some cases. While a single infusion of ketamine provided short-term relief, repeated doses maintained the antidepressant effects over a longer period. Ketamine administration was tolerated well, with the most common side effects being transient dissociative symptoms, dizziness, and nausea, which typically resolved within a few hours post-infusion.

Gamble et al. [120] in 2018 in randomized-controlled study examined the impact of ketamine-based anesthesia on ECT outcomes. They found that

Patients receiving ketamine-based anesthesia showed greater reduction in depressive symptoms compared to those receiving standard anesthesia. Enhanced ECT outcomes with ketamine suggest its potential as a beneficial adjunct in depression treatment.

Suprio Mandal et al.[121] in 2019 conducted a study to evaluate the efficacy of ketamine therapy in treating depression. The study included twenty-five male patients with severe depression who were either drug-free or drug-naïve. These patients had no other psychiatric or medical illness. Baseline assessments were performed, followed by the administration of ketamine hydrochloride at a dose of 0.5 mg/kg via IV bolus. Subsequent assessments were conducted one hour after the first dose, with a total of six doses administered over a two-week period. Assessments continued throughout the treatment period and concluded with a final assessment one month after the last dose. The results showed marked reduction in depression, anxiety, and overall severity of illness after two weeks and one month post-treatment. Notably, improvements in depression and anxiety were evident just one hour after the initial dose, although illness severity did not show immediate improvement. Some patients experienced transient adverse effects, which subsided within an hour. Hence concluded that ketamine produces a rapid and substantial antidepressant effect, which is noticeable immediately after administration and persists for up to one month.

Shin C, et al. [122] in 2020 conducted a study on ketamine in MDD: mechanisms and future perspectives. A series of recent randomized controlled trials have provided a high level of evidence for the therapeutic efficacy of ketamine treatment in MDD and presented new insights on the dose, usage, and route of administration of ketamine as an antidepressant. With this knowledge, it is anticipated that ketamine treatment protocols for MDD will be developed and implemented as a treatment option in clinical practice. However, long-term safety must be taken into consideration as ketamine has abuse potential and it is

associated with psychological side effects such as dissociative or psychotomimetic effects.

Paulo R. Shiroma et al.[123] in 2020, conducted a randomized, double-blind, active placebo-controlled study to compare the efficacy, safety, and durability of repeated versus single sub-anesthetic doses of ketamine for TRD. The study compared single versus six repeated ketamine infusions, using midazolam as an active placebo. Participants received either six ketamine infusions or five midazolam infusions followed by a single ketamine infusion over 12 days, with a follow-up period of up to six months. The primary goal was the decrease in MADRS score from baseline to 24 hours after the last infusion. Fifty-four participants completed all six infusions. There was no marked difference in the change of MADRS scores between the six ketamine group and the single ketamine group 24 hours after the last infusion. However, repeated ketamine infusions showed greater antidepressant efficacy compared to midazolam after five infusions, before the single ketamine infusion. Remission and response rates favored the six ketamine infusions after the fourth and fifth infusions, respectively, compared to midazolam before receiving the single ketamine infusion. Among those who responded, the median time-to-relapse was nominally, but not statistically, different (2 weeks for the single ketamine group and 6 weeks for the six ketamine group). The repeated infusions were relatively well-tolerated. The study concluded that repeated ketamine infusions demonstrated greater antidepressant efficacy compared to midazolam after five infusions but did not show a significant difference in comparison to a single ketamine infusion added to midazolam at the end of 2 weeks. The authors suggest that increasing knowledge of ketamine's mechanisms should guide future studies to find the optimal dosing balance for maximum antidepressant efficacy with minimal exposure.

Włodarczyk A et al. [124] in 2021 conducted a study on 49 inpatients with MDD and bipolar disorder subjects receiving eight 0.5mg/kg of ketamine

intravenous infusions, with a duration of 40min each, as an add-on treatment to standard-of-care pharmacotherapy. The safety psychometrics assessed dissociation and psychomimetic symptomatology with the CADSS and BPRS. The significant differences in CADSS scores between measurements in course of the treatment were observed(P=.003). No significant differences between BPRS measurements were made after infusions. In each case, both BPRS and CADSS values dropped to the "absent" level within 1 hour from the infusion. Neither CADSS nor BPRS scores were associated with the treatment outcome. The study demonstrates a good safety profile of intravenous ketamine as an add-on intervention to current psychotropic medication in TRD. The abatement of dissociation was observed in time with no sequelae nor harm. The study provides no support for the association between dissociation and treatment outcome.

Rozet I, et al.[125] in 2021 conducted a study on Ketamine in depression and electroconvulsive therapy. A rapid onset antidepressive effect of ketamine and esketamine has been proven conclusively. The results of extensive basic science research of the mechanism of action of low-dose ketamine doses has led to an alternative hypothesis of the pathophysiology of depression and the development of a novel neurotrophic concept of depression. Further longitudinal studies are warranted to determine the safety and efficacy of repeated administration of ketamine and its analogs to prevent relapse and recurrence of depression.

Balachandran A, et al.[126] in 2022 conducted a systematic review on Efficacy of ketamine for comorbid depression and acute or chronic pain. This systematic review examined the literature on the efficacy of sub-anesthetic doses of ketamine in individuals experiencing comorbid depression and chronic pain (CDCP), as well as comorbid depression and acute pain (CDAP). A secondary objective was to provide an assessment of dosage, route, and adverse effects of ketamine treatment for CDCP and

CDAP. A literature search was conducted on MEDLINE, PsycINFO, and Embase databases, coupled with a manual screening of the bibliography sections of included articles. In addition, registered ongoing and planned trials were searched on Clinicaltrials.gov. The end date of the search was April 9th, 2022. Included studies assessed changes in depression and pain in patients receiving at least one sub-anesthetic dose of ketamine. Assessment of quality was conducted using the GRADE checklist. Of the 7 CDCP clinical trials, 3 reported a reduction in depression and pain, 3 reported a reduction in depression or pain only, and 1 reported no improvement in either comorbidity. Among the 7 CDAP clinical trials, 4 studies found improvements in depression and pain while the remaining 3 reported improvements in only one parameter. 10 of the 12 case studies and 2 of the 3 observational studies assessing CDCP and CDAP found improvements in pain and depression scores post-treatment with effects of variable duration. Preliminary evidence supports the efficacy of ketamine in treating CDCP and CDAP.

Rascón-Martínez DM, et al.[127] in 2022 conducted a RCT on effect of single infusion of ketamine on depressive symptoms in elderly patients undergoing ophthalmological surgery. Authors conducted a randomized, double-blind, comparative study in patients aged 60 and over who required ophthalmological surgery. Experimental group received 0.5 mg/kg ketamine, whereas the control group received NaCl solution at 0.9%. Both groups received a standardized regimen of conscious sedation. Depressive symptom severity was assessed using the Geriatric Depression Scale-Short Form (GDS-SF) before and after exposure to ketamine infusion; tolerability was also evaluated. ANOVA model examined the direction of changes in symptom severity of depression among groups. Results showed that 90 patients were randomized. A significant reduction in symptom severity was observed after ketamine infusion (mean change from baseline: -1.6 vs -0.3 in the control group; $p = 0.003$). No differences emerged between groups in the presence of

adverse effects with ketamine infusion. Authors concluded that single infusion of ketamine in elderly patients undergoing ophthalmological surgery showed improved depressive symptoms in the first 24 hours of exposure to the drug with a good tolerability profile.

Rhee TG, et al.[128] in 2022, conducted a systematic review and meta-analysis to compare the efficacy and safety of ketamine versus ECT in patients with MDD. This review included six clinical trials involving a total of 340 patients, with 162 receiving ECT and 178 receiving ketamine. All six studies were conducted with patients eligible for ECT in inpatient settings, and five of them were RCTs. The pooled SMD for depression symptoms indicated that ECT was more effective than ketamine, with an SMD of −0.69 (95% CI, P = .15). This suggests that ECT had a greater impact on reducing depression severity. However, the adverse effect profiles of ketamine and ECT differed. Ketamine was associated with lower risks of headache and muscle pain, while ECT had lower risks of blurred vision, vertigo, diplopia/nystagmus, and transient dissociative/depersonalization symptoms.

Ahuja et al.[129] in 2022, conducted a retrospective descriptive cohort study to evaluate the clinical characteristics, treatment patterns, outcomes, and safety of IM ketamine treatment in 452 patients at a private outpatient psychiatric clinic network in the United States between January 2018 and June 2021. The patients had an average of 2.8 psychiatric diagnoses. The majority (93%) had MDD, 54% had GAD, and 28% had PTSD. Patients received a median of 4 IM ketamine treatments, ranging from 1 to 48. Significant improvements were observed in both depression and anxiety scores. Median PHQ-9 scores decreased by 38%, from 16.0 at baseline to 10.0 at the last treatment, and median GAD-7 scores decreased by 50%, from 14.0 to 7.0. These improvements were maintained for over 7 months during the maintenance phase. The percentage of patients reporting suicidal ideation decreased from 60% at baseline to 47% at the last treatment.

Zheng W, et al.[130] [2022] in their randomized, double-blind, placebo-controlled trial involving 135 patients with depression (68 males, 67 females), received 6 intravenous infusions of ketamine (0.5 mg/kg over 40 minutes) over a period of two weeks. The study found no significant difference in antianhedonic response rates (50% vs. 47.8%, $p > 0.05$) or remission rates (26.5% vs. 14.9%, $p > 0.05$) between males and females. A linear mixed model showed a nonsignificant between-group difference in MADRS anhedonia subscale scores [$F(1,132.5) = 1.1$, $p = 0.30$]. However, females reported a significantly larger reduction in anhedonic symptoms than males at the 2-week follow-up ($p < 0.05$). The study concluded that the rates of antianhedonic response and remission to multiple ketamine infusions for treating depression were similar between males and females. These findings should be verified by future studies, preferably RCTs.

Hassan K, et al. [131] in 2022 analysed safety, effectiveness and tolerability of sublingual ketamine in depression and anxiety. Intake scores on the Generalized Anxiety Disorder Screener (GAD-7) and Patient Health Questionnaire (PHQ-9) were compared to scores after treatments of three doses of ketamine RDT, and after six doses of ketamine RDT. After three doses of SL ketamine, 47.6% of patients showed a significant reduction in PHQ-9 scores, and 47.6% of patients showed a marked decrease in GAD-7 scores. Reduction rates were higher in those patients who completed a clinically recommended six doses of RDT ketamine. This study demonstrates that SL ketamine is a novel, safe, and effective treatment for TRD and treatment-resistant anxiety. SL ketamine offers an alternative therapeutic approach to IV ketamine when treating those with TRD.

Sachdeva B, et al. [132] in 2023 conducted a study on ketamine as a therapeutic agent in MDD and PTSD: potential medicinal and deleterious effects. MDD and PTSD are the most common causes of emotional distress that impair an individual's quality of life. MDD is a chronic mental illness that affects 300 million people across the world. Clinical

manifestations of MDD include fatigue, loss of interest in routine tasks, psychomotor agitation, impaired ability to focus, suicidal ideation, hypersomnolence, altered psychosocial functioning, and appetite loss. Individuals with depression also demonstrate a reduced behavioral response while experiencing pleasure, a symptom known as anhedonia. Like MDD, PTSD is a prevalent and debilitating psychiatric disorder resulting from a traumatic incident such as sexual assault, war, severe accident, or natural disaster. Symptoms such as recalling event phases, hypervigilance, irritability, and anhedonia are common in PTSD. Both MDD and PTSD pose enormous socioeconomic burdens across the globe. The search for effective treatment with minimal side effects is still ongoing. Ketamine is known for its anesthetic and analgesic properties. Psychedelic and psychotropic effects of ketamine have been found on the nervous system, which highlights its toxicity.

Schwartz OS, et al.[133] in 2023 published a study protocol for a RCT of low-dose ketamine for young people with major depressive disorder on the Study of Ketamine for Youth Depression (SKY-D). SKY-D is a double-masked, RCT government's National Health and Medical Research Council (NHMRC). Participants aged between 16 and 25 years (inclusive) with moderate- to-severe MDD will be randomised to receive either low-dose ketamine (intervention) or midazolam (active control) via subcutaneous injection once per week for 4 weeks. The primary outcome is change in depressive symptoms on the MADRS after 4 weeks of treatment. Further follow-up assessment will occur at 8 and 26 weeks from treatment commencement to determine whether treatment effects are sustained and to investigate safety outcomes.

Azari L, et al.[134] in 2023 conducted a systematic review on the efficacy and safety of ketamine for depression in patients with cancer. Authors reviewed the published literature in MEDLINE® (via PubMed®), EMBASE, and Scopus from 1 January 1982 to 20 October 2022. Authors screened the retrieved abstracts against inclusion criteria and conducted a full-text

review of eligible studies. Following extraction of data from included studies, we used a framework analysis approach to summarize the evidence on using ketamine in patients with cancer. Results showed that all 5 included studies were RCTs conducted in inpatient settings in China. In all included studies ketamine was administered intravenously. Three studies used only racemic ketamine, and two studies used both S-ketamine and racemic ketamine. All included studies reported ketamine a tolerable and effective drug to control depression symptoms. Authors concluded that included studies showed administration of sub-anesthesia ketamine significantly improves post-operative depression among patients with cancer.

Nikolin S, et al.[135] in 2023 conducted a systematic review and meta-analysis on Ketamine for the treatment of major depression. In this systematic review and meta-analysis, we searched Embase, Medline, Pubmed, PsycINFO, and CENTRAL up to April 13, 2023, for randomised controlled trials (RCTs) investigating ketamine for depression. Two investigators independently assessed study eligibility and risk of bias and extracted the data on depression severity scores, response and remission rates, and all-cause dropouts. Multivariable mixed-effects meta-regressions incorporated drug formulation (racemic (Rac) or esketamine (Esket)) and dose (Low or High) as covariates. Treatment effects were assessed: immediately following the first dose, during further repeated dosing, and follow- up after the final dose of a treatment course. This study is registered with PROSPERO (CRD42021221157). Findings The systematic review identified 687 articles, of which 49 RCTs were eligible for analysis, comprising 3299 participants. Standardised mean differences (95% confidence intervals) immediately following the first/single treatment were moderate-high for all conditions (Rac-High: −0.73, −0.91 to −0.56; Esket-High: −0.48, −0.75 to −0.20; Rac-Low: −0.33, −0.54 to −0.12; Esket-Low: −0.55, −0.87 to −0.24). Ongoing effects during repeated dosing were significantly greater than the control for Rac-High (−0.61; −1.02 to −0.20)

and Rac-Low (−0.55, −1.09 to −0.00), but not Esket-Low (−0.15, −0.49 to 0.19) or Esket-High (−0.22, −0.54 to 0.10). At follow-up effects remained significant for racemic ketamine (−0.65; −1.23 to −0.07) but not esketamine (−0.33; −0.96 to 0.31). All-cause dropout was similar between experiment and control conditions for both formulations combined (Odds Ratio = 1.18, 0.85–1.64). Overall heterogeneity varied from 5.7% to 87.6% Interpretation of findings suggested that effect sizes for depression severity, as well as response and remission rates, were numerically greater for racemic ketamine than esketamine. Higher doses were more effective than low doses. Differences were evident in initial effects, ongoing treatment, and lasting effects after the final dose.

Geller J, et al. [136] in 2023 conducted a study on response to ketamine treatment for MDD not associated with number of psychiatric comorbidities. A retrospective review of medical records from a community ketamine clinic was done. Statistical analyses compared response to intravenous ketamine treatment, as defined by a 50% reduction in Patient Health Questionnaire (PHQ-9) score or final score of <10, in patients with an isolated diagnosis of MDD to those with comorbid GAD, OCD, PTSD and/or ADHD. Results showed that data from 129 patient were analyzed (55.8 % female). It was determined that the number of psychiatric comorbidities did not correlate with the response rate to ketamine treatment or with the average change in PHQ-9 scores. Authors concluded that these findings suggest ketamine may be an effective treatment for depression in appropriate patients with psychiatric comorbidities including GAD, OCD, PTSD and/or ADHD. Additional investigation is warranted to evaluate various patient-level and other factors that may impact ketamine's ability to attenuate depressive symptoms.

Vasiliu O, et al.[137] in 2023 done a review of clinical evidence w.r.t. Esketamine for TRD. A total of 14 papers were reviewed, and their results support the recommendation of esketamine for treatment of TRD as an

add on to antidepressants. It was found that there have been a few trials which did not report a significant effect on the severity of depressive symptoms with esketamine in TRD. There has been insufficient data to formulate specific guidelines about esketamine administration because evidence about favorable or negative prognostic factors of this treatment has been lacking, and the duration of its administration has not been unanimously accepted. Novel directions for research have been identified, especially in the case of patients with TRD and substance use disorders, geriatric or bipolar depression or in major depression with psychotic features.

Anand, A. et al.[138] in 2023 evaluated ketamine versus ECT for nonpsychotic TRD. A total of 403 patients underwent randomization at five clinical sites; 200 patients were assigned to the ketamine group and 203 to the ECT group. After 38 patients had withdrawn before initiation of the assigned treatment, ketamine was administered to 195 patients and ECT to 170 patients. 55.4% of the patients in the ketamine group and 41.2% of those in the ECT group had a response ($P<0.01$ for the non-inferiority of ketamine to ECT). ECT appeared to be associated with a decrease in memory recall after 3 weeks of treatment (mean [±SE] decrease in the T-score for delayed recall on the Hopkins Verbal Learning Test–Revised, −0.9±1.1 in the ketamine group vs. −9.7±1.2 in the ECT group; scores range from −300 to 200, with higher scores indicating better function) with gradual recovery during followup. Improvement in patient-reported quality-of-life was similar in the two trial groups. ECT was linked to musculoskeletal adverse effects, while ketamine was associated with dissociation. The authors concluded that ketamine was non-inferior to ECT as a treatment for treatment-resistant major depression without psychosis.

Seemüller, F et al.[139] in their study, the psychometric properties of the HAMD, MADRS, and the BDI were compared. This post-hoc analysis used prospectively collected data from a naturalistic study involving 1,014

inpatients diagnosed with major depression. All three scales showed good to very good internal consistency. The HAMD-17 revealed four distinct factors: "anxiety," "depression," "insomnia," and "somatic." The MADRS also displayed four factors: "sadness," "neurovegetative," "detachment," and "negative thoughts." The BDI identified three factors: "negative attitude towards self," "performance impairment," and “somatic." The high correlation between individual items and the total MADRS score underscored the scale’s excellent reliability. Compared to the HAMD, the MADRS might be more effective in detecting or measuring treatment effects within a homogeneous sample.

Brody BD, et al. [140] in 2024 conducted a study on ketamine for MDD during an inpatient psychiatric admission: effectiveness, adverse events, and lessons learned. Authors performed a retrospective chart review of inpatients with non-psychotic MDD treated during the initial 3 years of a ketamine infusion program. Treatment effectiveness was defined using change in MADRS scores over five infusions. MDD treatment response was defined by a 50% reduction of MADRS score, and remission was defined as MADRS score≤10 at any point during the treatment. We also report the frequency of adverse events. Results showed that 41 patients with MDD were treated and had outcome data. 19 patients (46.5%) met criteria for response and 15 patients (26.5%) met criteria for remission during treatment. Four patients (10%) had adverse psychological or behavioural outcomes. Authors concluded that twice weekly racemic ketamine infusion is an effective treatment option for patients hospitalized with MDD. Unmonitored or at home ketamine therapy may pose substantial risks.

Arvind BA et al. [141] in their study provides an extensive analysis of the burden of depressive disorders (DD) in India.This study is part of the National Mental Health Survey (NMHS) of India conducted in 2015-2016, aiming to estimate the prevalence and patterns of depressive disorders across 12 states in India. The study found that the lifetime prevalence of

depressive disorders in India is 5.25%, while the current prevalence is 2.68%. Depressive disorders in India are more prevalent among females and the productive age group (30-59 years).The relationship between urbanization and depression has been inconsistent in the literature. The NMHS reported higher prevalence rates in urban areas, especially in cities with populations exceeding one million.

Poongothai et al.[142]. in 2009 conducted a study which provides essential epidemiological data on the prevalence of depression in an urban Indian population, highlighting the significant burden of depression and the need for tailored mental health services. The study highlighted that the prevalence of depression was influenced by various demographic factors, including age, sex, marital status, education, and income.

Bonnett et al.[143] in their study involved 40 sequential patients diagnosed with MDD. The treatment protocol included six IM ketamine sessions, with doses tailored to each patient's response. Psychological assessments using the PHQ-9, PCL-5, and GAD-7 were conducted before the first and after the sixth session to measure changes in symptoms.The results indicated significant reductions in depressive symptoms, PTSD symptoms, and anxiety levels. Specifically, the PHQ-9 scores showed a 55% reduction, PCL-5 scores decreased by 51%, and GAD-7 scores also dropped by 51%. These results are comparable to those reported in studies on IV ketamine, suggesting that IM ketamine is similarly effective.

Pennybaker et al.[144] (2021) investigated a study to know the impact of age on the effectiveness of ketamine infusions for treating MDD. Researchers used a linear-mixed model to compare the relationship between age and percent change in Beck Depression Inventory (BDI-II) scores across six serial ketamine infusions (administered twice weekly for 3 weeks). A significant interaction between age and infusion number ($F = 3.01$, $p = .0274$) indicated that the relationship between age and treatment response varied with the infusion number. Follow-up tests revealed that younger age significantly predicted greater clinical improvement at the

fourth infusion (t = 3.02, p = .004); this relationship was weaker at the fifth infusion (t = 1.95, p = .057) and absent by the sixth infusion. Age was not a significant predictor of treatment durability, defined as the percent change in BDI-II scores three weeks after the sixth infusion. These findings suggest that younger age is associated with a faster response to six serial ketamine infusions, but by the sixth infusion and during subsequent follow-up weeks, age no longer predicts ketamine's antidepressant effects. Age may influence the speed but not the durability or overall efficacy of ketamine treatment, indicating that different mechanisms may underlie various aspects of ketamine's antidepressant activity.

Pathak U, et al. [145] in 2021, conducted a RCT with sixty patients aged 18–60 years of depressive disorder and MSSI score greater than 20. Patients with severe medical or surgical illnesses, pregnancy, and breastfeeding females were excluded. Participants were divided into either the ketamine group or the normal saline group. Three infusions were administered over one week on day 0, day 2, and day 4. Baseline assessments were made using the 17-item HAM-D17 and the MSSI for depression and suicidality, respectively. Significant reductions in HAM-D17 and MSSI scores were observed within 6 hours of the first dose in the ketamine group compared to the normal saline group. The ketamine group also showed significant sustained improvement on subsequent days up to one week compared to the normal saline group.

MATERIAL AND METHODS

The study was conducted for a period of one year on patients diagnosed with MDD presenting to DMC&H, Ludhiana.

CTRI Registration number: CTRI/2024/07/070304

Source of Data

Sample Collection:- This study comprised 90 patients in the age group 18-65 diagnosed with MDD as per International Classification of Diseases (ICD-11) who had been taking one class of antidepressant (Escitalopram 10-20 mg) for at least 4 weeks. After obtaining informed consent, they were admitted as indoor patients and further randomized into 3 groups of 30 patients each. Group A comprised 30 patients who received intravenous Ketamine, Group B (n=30) received intramuscular Ketamine, and Group C (n=30) acted as the control group.

Method of Collection of Data

Inclusion Criteria:

- Patients seeking treatment at the Department of Psychiatry, Dayanand Medical College & Hospital (DMCH), Ludhiana.
- Both males and females aged 18-65 years.
- Primary diagnosis of MDD without psychotic features based on DSM-5.
- Diagnosis of moderate-severe MDD defined by MADRS ≥ 20.
- Patients who had been taking escitalopram 10-20 mg for at least 4 weeks.
- Medically stable for study participation.

Exclusion Criteria:

- Any other major psychiatric disorder in patients with MDD
- History of any known uncontrolled medical condition.
- Women who were pregnant or lactating.
- Patients who did not give consent for the study.
- Untreated hypertension (Systolic BP > 140 mmHg and/or Diastolic BP > 90 mmHg).

Methodology:The study was conducted on 90 patients diagnosed with MDD as per International Classification of Diseases (ICD-11) who had been taking at least one class of antidepressant (escitalopram 10-20 mg) for a minimum period of 4 weeks, presenting to the Department of Psychiatry, DMC&H Ludhiana. Patients met the inclusion criteria and provided written informed consent before enrollment.

Study Design:-

The study was a randomized, double-blinded, placebo-controlled, pre and post-intervention assessment study carried out on 90 patients. Patients meeting the inclusion criteria were randomly allocated into three groups:

Group-A:- Subjects received ketamine hydrochloride (0.5 mg/kg) intravenous infusion dissolved in 100 ml normal saline via infusion pump over 40 minutes, two infusions per week for two weeks as augmentation to the ongoing antidepressant regimen.

Group-B:- Subjects received ketamine hydrochloride (0.5 mg/kg) intramuscularly, two injections per week for two weeks as augmentation to the ongoing antidepressant regimen.

Group-C:- Subjects acted as the control group and did not receive any ketamine.

The severity of depression was assessed using the MADRS. Patients underwent prospective observation. Vitals (blood pressure, heart rate, etc.) were monitored every 5 minutes throughout the time of infusion and every half hour for 2 hours after infusion. The clinical response to ketamine administration in depressive patients was assessed by MADRS pre-infusion and post-infusion every 4 hours. The patients were discharged after being assessed on the Modified Aldrete Score. Thereafter, subjects were followed up for two weeks. Patients were informed that they were free to withdraw from the study at any time without ramifications on their relationship with the healthcare provider.

TOOLS-

MADRS- It was developed by SA Montgomery and M Asberg in 1979 with the aim of constructing a scale which would be sensitive to treatment effects of anti- depressants. It is a 10 item diagnostic questionnaire used to measure the severity of depressive episodes in patients with mood disorders. The items are rated on a continuum of 0-6.The questionnaire includes questions on following symptoms –

1. Apparent sadness
2. Reported sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

The interpretation of scale is as follows-

- **0-6**- Normal/ Symptoms absent
- **7-19**- Mild Depression
- **20-34**- Moderate Depression
- **>34**- Severe Depression

CLINICIAN-ADMINISTERED DISSOCIATIVE STATES SCALE (CADSS)

The Clinician-Administered Dissociative States Scale (CADSS) is a reliable and valid instrument for measuring present-state dissociative symptoms. It includes 27 items, with 19 rated by the subject and 8 by an observer. The subjective component, administered by a clinician, consists of 19 items, each prefaced with "at this time," followed by the item. Subjects respond on a scale from 0 = not at all, 1 = slightly, 2 = moderately, 3 = considerably, 4 = extremely. The clinician records the subject's response and moves to the next item. The observer component

includes eight behavioral items identified in clinical literature as indicative of dissociative states. High Cronbach alpha values from studies on ketamine effects indicate that the CADSS is internally consistent for assessing ketamine-induced dissociation in clinical trials for anxiety, though it does not capture symptoms such as thought disorder.

MODIFIED ALDRETE SCORING: The modified Aldrete score is used to evaluate patients from the Post Anaesthesia Care Unit (PACU), with the purpose to check whether they can be safely discharged. The score accounts for consciousness, mobility, breathing, circulation, and O2 saturation. The total modified Aldrete score values range from 0 to 12. Scores closer to 0 indicate that the patient is closest to the anesthesia state. Scores of 9 and above indicate that the patient can be discharged and the closer the score is to 12, the higher the chances for all anestethic, regardless of administering method, to have worn off.

STATISTICAL ANALYSIS

Data were described in terms of range; mean ± standard deviation (± SD), median, frequencies (number of cases), and relative frequencies (percentages) as appropriate. To determine whether the data were normally distributed, a Kolmogorov-Smirnov test was used. Comparison of quantitative variables between the study groups was done using ANOVA and Kruskal-Wallis Test with post hoc Tukey's for independent samples for parametric and non-parametric data, respectively. For comparing categorical data, Chi-square ($\chi 2$) test was performed, and Fisher's exact test was used when the expected frequency was less than 5. A probability value (p value) less than 0.05 was considered statistically significant. The paired t-test was used to confirm the differences between baseline MADRS and post KET T- 4-hour values. The relationship between variables was evaluated using Spearman's rank correlation analysis. All statistical calculations were done using the Statistical Package for the Social Sciences (SPSS) version 21 (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

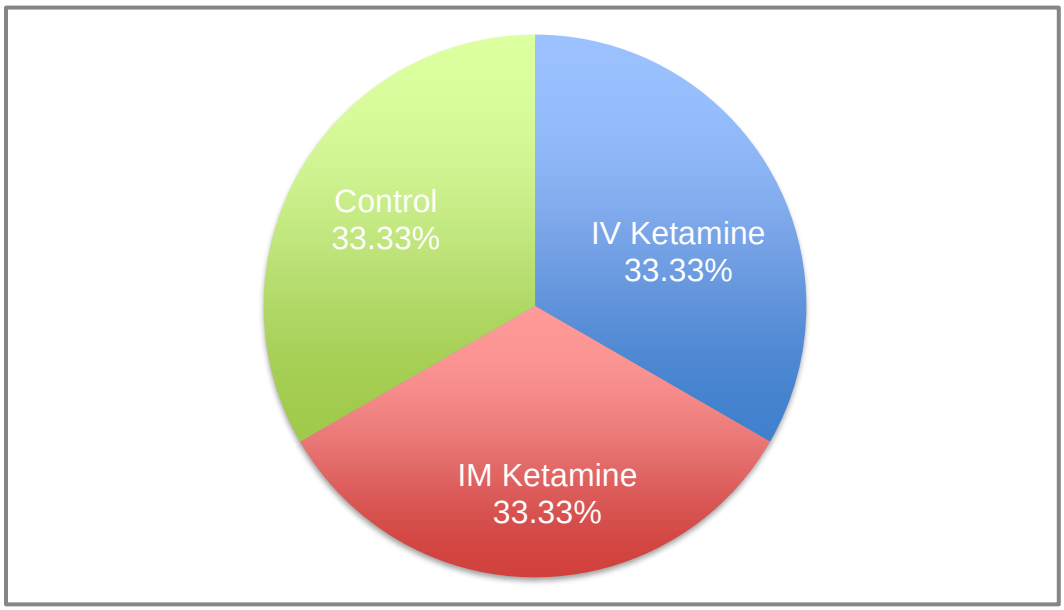
OBSERVATION AND RESULTS

The present study was carried out to compare the therapeutic efficacy of ketamine given by intravenous route versus intramuscular route in patients of MDD.

Table 1: Shows the group-wise distribution of patients enrolled in the study.

SN	Group	Description	No. of cases	Percentage
1	A	KETAMINE (0.5mg/kg IV infusion in 100 ml normal saline via infusion pump over 40 minutes)	30	33.33
2	B	KETAMINE (0.5mg/kg IM)	30	33.33
3	C	Control (not receiving ketamine)	30	33.33

Figure 2: Shows the group-wise distribution of patients enrolled in the study.



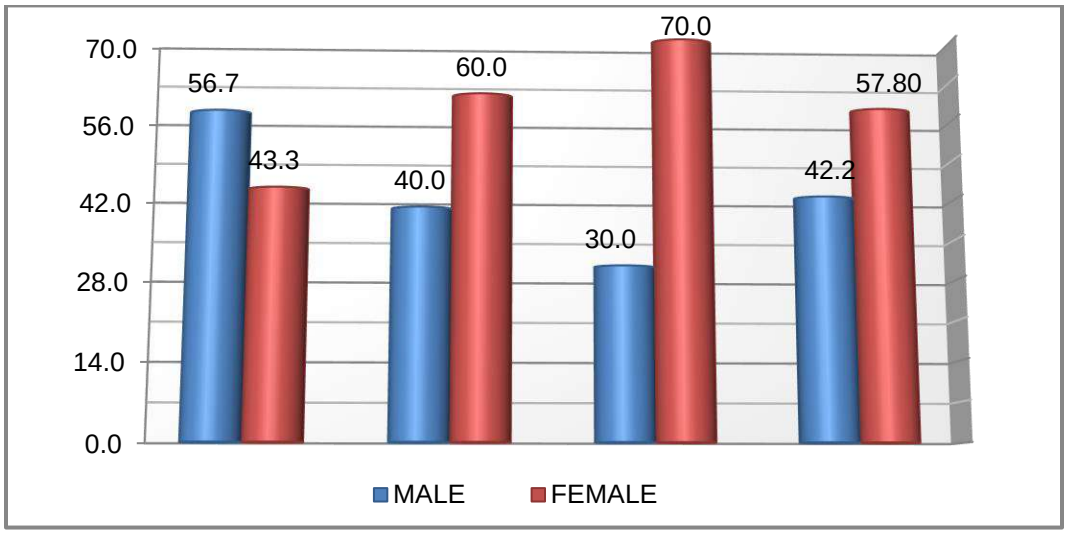
Out of total of 90 patients enrolled for the study Group A, n= 30 (33.33%) received IV ketamine, Group B, n= 30 (33.33%) received IM ketamine and Group C, n=30 (33.33%) will act as control group.

Table 2: As depicted in Table 2, the subjects in the three groups were divided according to gender. The Chi-square (χ^2) test was employed to assess gender distribution differences among the groups. The majority of subjects in the control group were males. In the IM group, a majority of females was noted, and the same findings were observed in the IV group.

Table 2: Gender distribution among the study subjects.

Group	**Male**		**Female**		**Total**		**χ^2**	**p- value**
	N	**%**	**N**	**%**	**N**	**%**		
Control	17	56.7	13	43.3	30	100	4.46	0.11
IM	12	40.0	18	60.0	30	100		
IV	9	30.0	21	70.0	30	100		
Total	38	42.2	52	57.8	90	100		

Figure 3: Gender distribution among the study subjects.



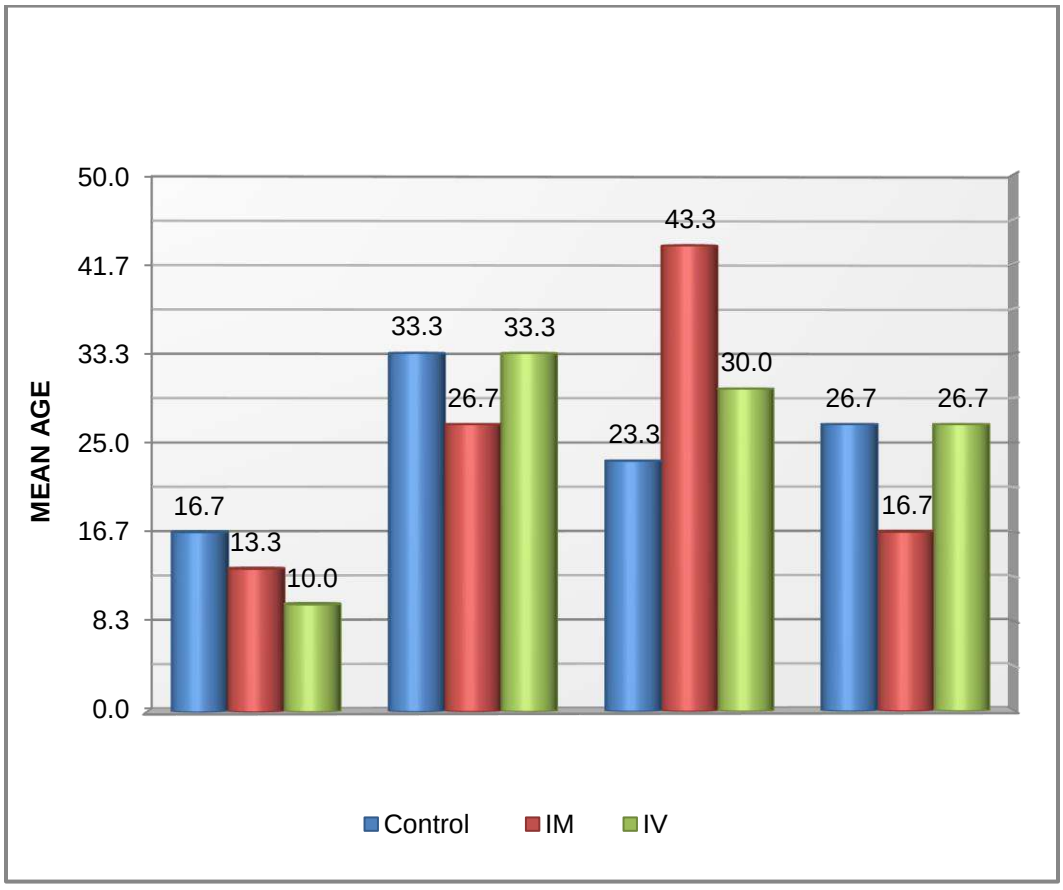
The majority of subjects in control group are males (56.7%), with a lesser number of females (43.3%). In IM Group**:** The majority of subjects are females (60%), with fewer males (40%). In IV Group**:** the majority of subjects are females (70%), with fewer males (30%).

Table 3 presents a comparative analysis of age distribution among three groups: Control, IM (Intramuscular), and IV (Intravenous). It includes the Chi-square (χ^2) test value and p-value to assess the statistical significance of age distribution differences. Additionally, the mean and standard deviation (SD) of age are reported for each group. The 35-44 age range is most common in the Control and IV groups, while the 45-54 age range is most common in the IM group**.**

Table 3: Mean age among the study subjects

Group	**Control**		**IM**		**IV**		**χ^2**	**p-value**
	N	**%**	**N**	**%**	**N**	**%**		
25-34	5	6.7	4	13.3	3	10.0		
35-44	10	33.3	8	26.7	10	33.3		
45-54	7	23.3	13	43.3	9	30.0	3.57	0.73
>54	8	26.7	5	16.7	8	26.7		
Total	30	33.3	30	33.3	30	33.3		
Mean±SD	44.9±9.92		45.17±8.60		43.13±8.16			

Figure 4: The age distribution of participants across three groups: Control, IM (Intramuscular), and IV (Intravenous).



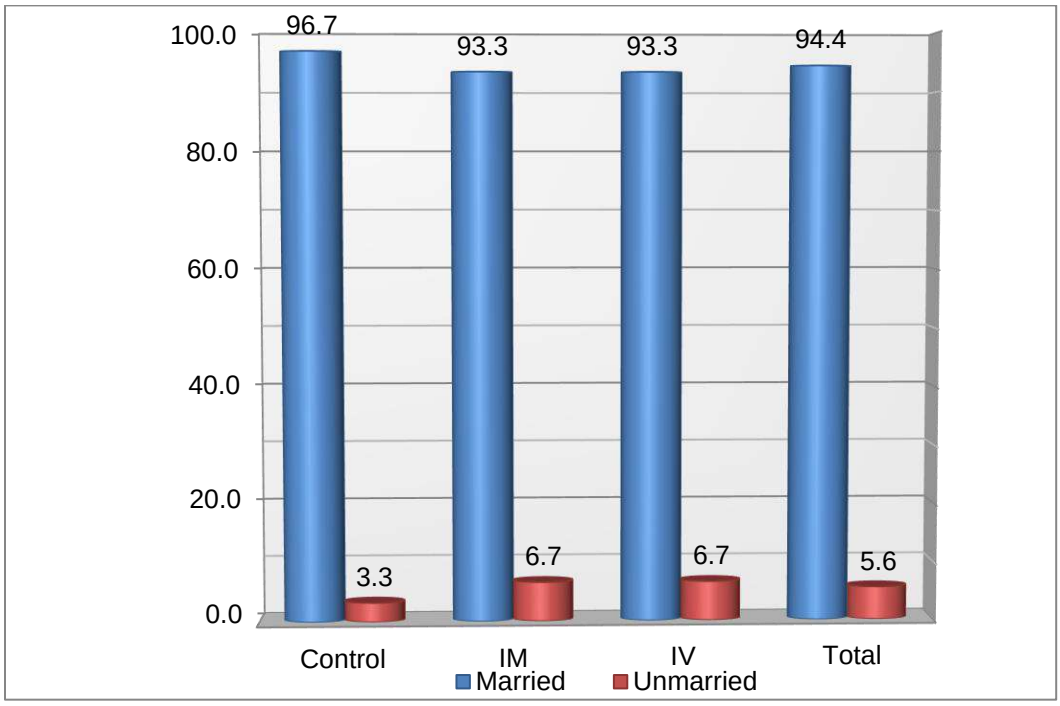
It highlights that the 35-44 age range is the most common in the Control and IV groups, while the 45-54 age range is the most common in the IM group.

Table 4 presents a comparative analysis of marital status (Married vs. Unmarried) across three groups: Control, IM (Intramuscular), and IV (Intravenous). It includes the Chi-square (χ^2) test value and p-value for statistical significance. The Control group has the highest percentage of married participants (96.7%), while both the IM and IV groups have 93.3% married participants.

Table 4: Marital status among the study subjects

Group	**Married**		**Unmarried**		**Total**		**χ^2**	**p-value**
	N	**%**	**N**	**%**	**N**	**%**		
Control	29	96.7	1	3.3	30	100	0.42	0.81
IM	28	93.3	2	6.7	30	100		
IV	28	93.3	2	6.7	30	100		
Total	85	94.4	5	5.6	90	100		

Figure 5: Marital status among the study subjects.



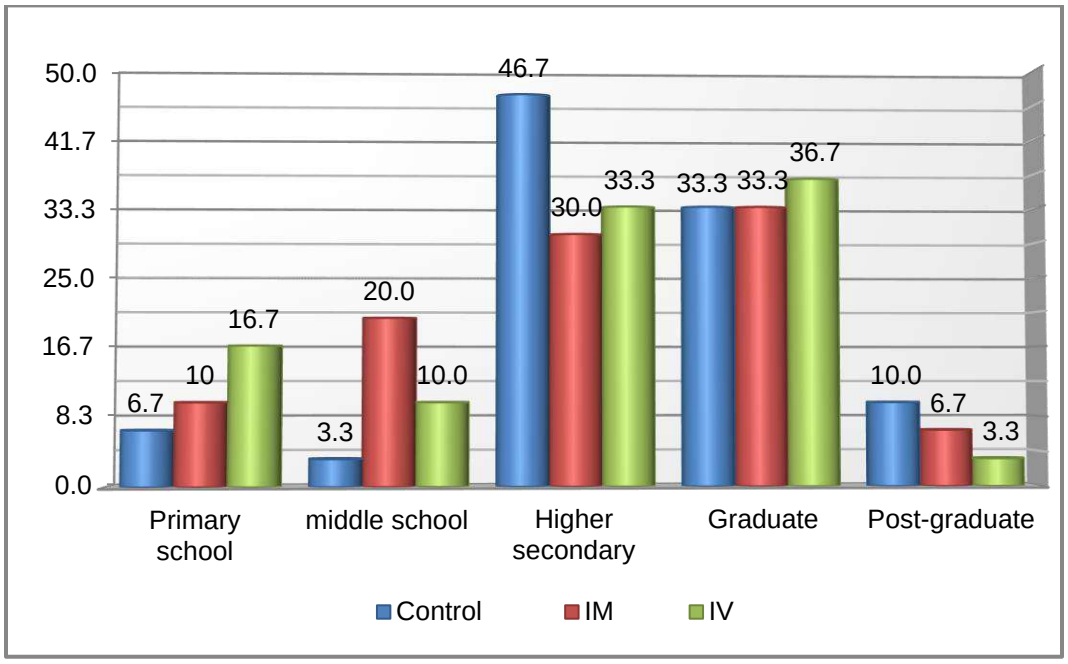
The majority of subjects are married (94.4%), with a significantly smaller number are unmarried (5.6%) in 90 patients.

Table 5 shows the educational level distribution across Control, IM (Intramuscular), and IV (Intravenous) groups, including Chi-square (χ^2) test results for statistical significance. In the Control group, 46.7% completed Higher Secondary School and 33.3% are Graduates. In the IM group, 33.3% are Graduates, 30.0% completed Higher Secondary School, and 20.0% have Middle School education. In the IV group, 36.7% are Graduates and 33.3% completed Higher Secondary School. Most participants in each group have at least completed Higher Secondary School.

Table 5: Education among the study subjects

Group	Control		IM		IV		Total.		χ^2	p-value
	N	%	N	%	N	%	N	%		
Primary School	2	6.7	3	10.0	5	16.7	10	11.1	7.35	0.48
Middle School	1	3.3	6	20.0	3	10.0	10	11.1		
Higher Secondary School	14	46.7	9	30.0	10	33.3	33	36.7		
Graduate	10	33.3	10	33.3	11	36.7	31	34.4		
Postgraduate	3	10.0	2	6.7	1	3.3	6	6.7		

Figure 6: Education among the study subjects.



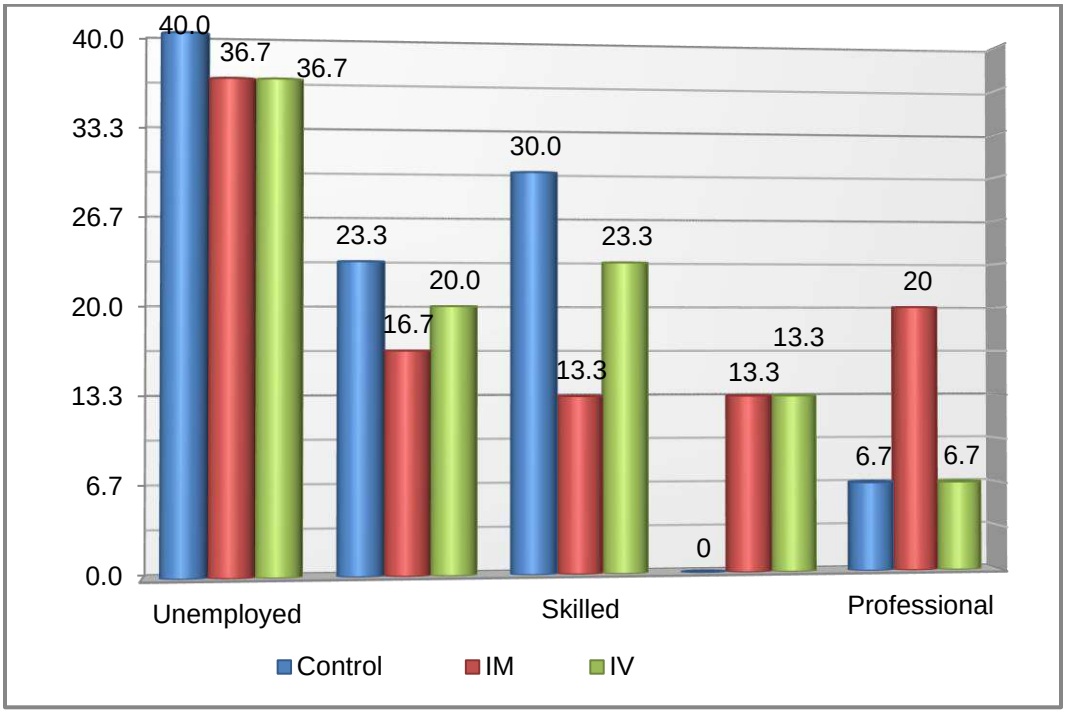
The majority of participants across all groups have at least completed Higher Secondary School education. A substantial number of participants are Graduates. The proportion of participants with Postgraduate education is relatively low across all groups.

Table 6 presents a comparative analysis of occupational distribution among Control, IM (Intramuscular), and IV (Intravenous) groups, including Chi-square (χ^2) test results and p-values for statistical significance. The majority of participants in all groups were unemployed: 40% in the Control group, and 36.67% in both the IM and IV groups.

Table 6: Occupation among the study subjects

Group	Control		IM		IV		Total		χ^2	p-value
	N	%	N	%	N	%	N	%		
Unemployed	12	40.0	11	36.7	11	36.7	34	37.8	9.54	0.29
Semi-skilled	7	23.3	5	16.7	6	20.0	18	20.0		
Skilled	9	30.0	4	13.3	7	23.3	20	22.2		
Semi-professional	0	0.0	4	13.3	4	13.3	8	8.9		
Professional	2	6.7	6	20.0	2	6.7	10	11.1		

Figure 7: Occupation among the study subjects.



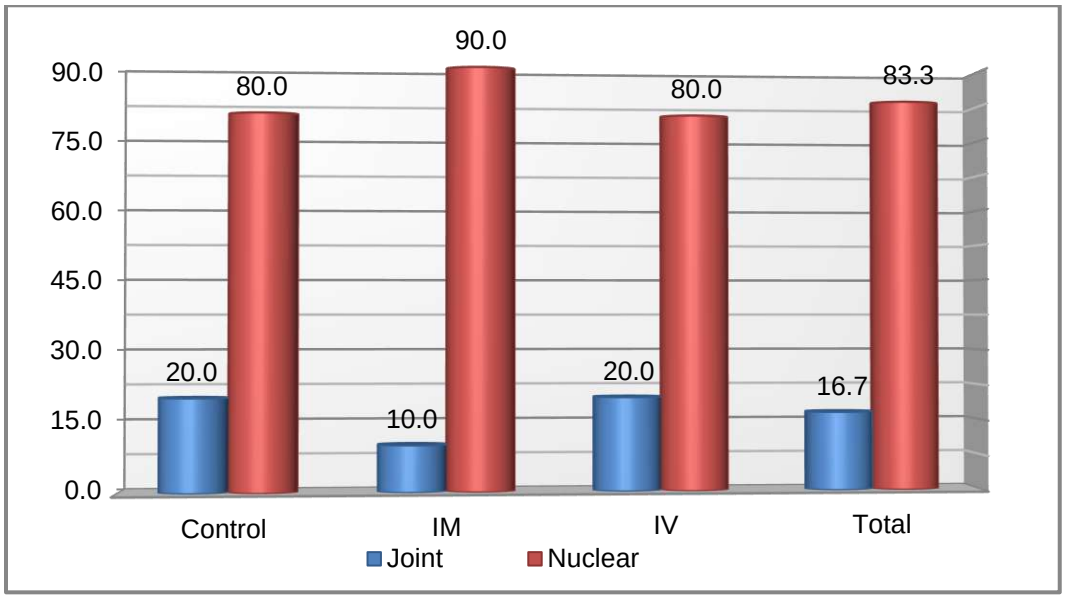
The highest proportion of participants across all groups is in the Unemployed category. Significant numbers of participants are also found in the Skilled and Semi-skilled categories. There is a relatively lower representation of Semi-professional and Professional participants across all groups.

Table 7 presents a comparative analysis of family structure (Joint vs. Nuclear) across Control, IM (Intramuscular), and IV (Intravenous) groups, including Chi-square (χ^2) test results and p-values for statistical significance. Most participants are from Nuclear families (83.3% overall). The IM group has the highest percentage of Nuclear family participants (90.0%), while the Control and IV groups each have 80.0% from Nuclear families. Only 16.7% are from Joint families across all groups.

Table 7: Type of family among the study subjects

Group	Joint		Nuclear		Total		χ^2	p-value
	N	%	N	%	N	%		
Control	6	20.0	24	80.0	30	100	1.44	0.49
IM	3	10.0	27	90.0	30	100		
IV	6	20.0	24	80.0	30	100		
Total	15	16.7	75	83.3	90	100		

Figure 8: Type of family among the study subjects.



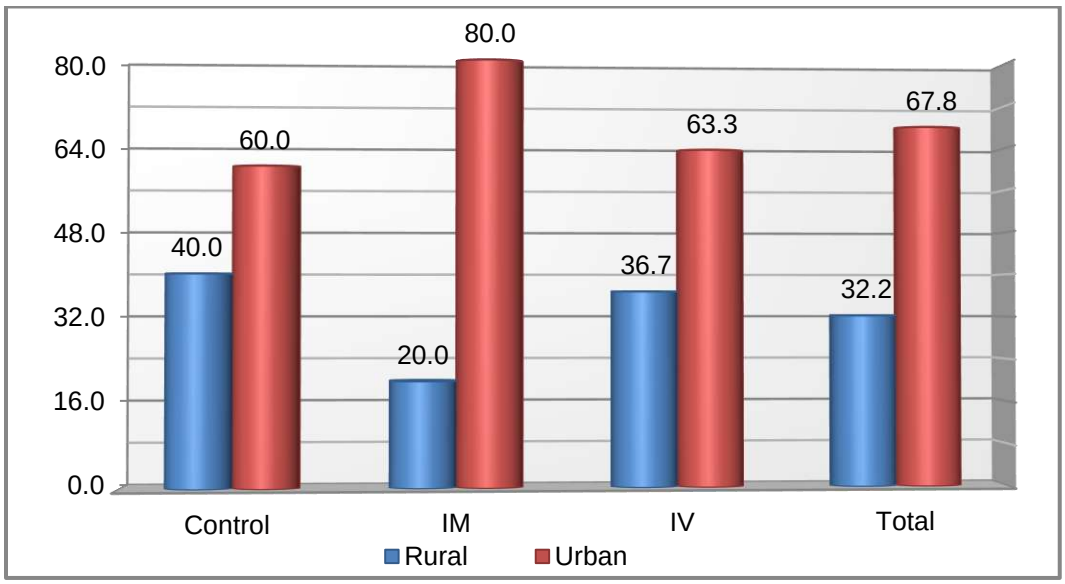
The figure shows that in all three groups (Control, IM, IV), the majority of participants are from Nuclear families (red bars), with a smaller proportion from Joint families (blue bars).

Table 8 presents a comparative analysis of residential distribution (Rural vs. Urban) across Control, IM (Intramuscular), and IV (Intravenous) groups, including Chi-square (χ^2) test results and p-values for statistical significance. Urban participants are the majority in all groups: 80.0% in the IM group, 63.3% in the IV group, and 60.0% in the Control group. Overall, 67.8% of participants are from urban areas and 32.2% are from rural areas.

Table 8 : Locality among the study subjects

Group	Rural		Urban		Total		χ^2	p-value
	N	%	N	%	N	%		
Control	12	40.0	18	60.0	30	100	3.15	0.26
IM	6	20.0	24	80.0	30	100		
IV	11	36.7	19	63.3	30	100		
Total	29	32.2	61	67.8	90	100		

Figure 9: Distribution of Rural and Urban family observations across three groups (Control, IM, IV).



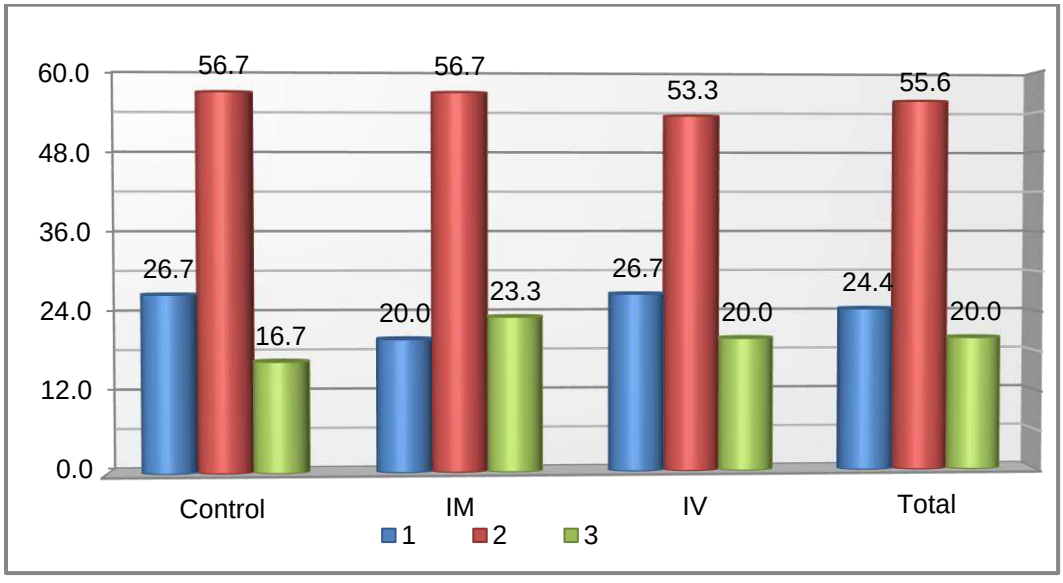
In all groups, Urban population observations are higher than Rural population observations.

Table 9 presents the distribution of patients by the number of depressive episodes across Control, IM (Intramuscular), and IV (Intravenous) groups, along with Chi-square (χ^2) test results. Most patients experienced 2 depressive episodes (55.6%), followed by 1 episode (24.4%), and 3 episodes (20.0%).

Table 9: Number of lifetime episodes of depression among the study subjects

Group	1		2		3		χ^2	p-value
	N	%	N	%	N	%		
Control	8	26.7	17	56.7	5	16.7	0.95	0.62
IM	6	20.0	17	56.7	7	23.3		
IV	8	26.7	16	53.3	6	20.0		
Total	22	24.4	50	55.6	18	20.0		

Figure 10: Number of lifetime episodes of depression among the study subjects.



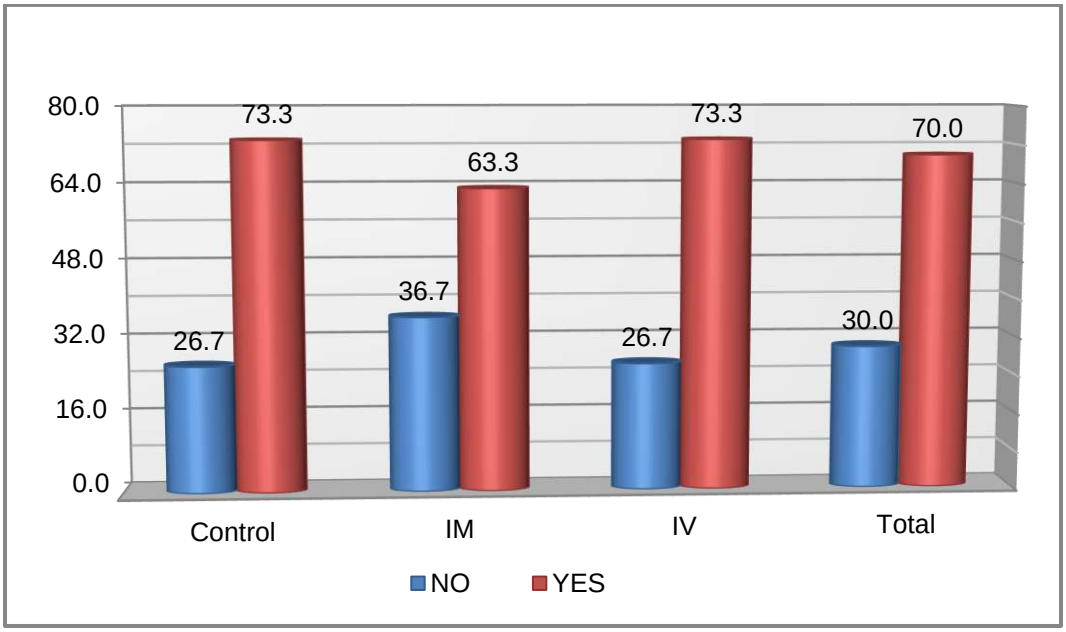
The highest number of participants in control and IM groups experienced 2 depressive episodes (56.7%) whereas in IV group also maximum patients experienced 2 depressive episodes (53.3%).

Table 10: Presents the distribution of patients based on their family history of psychiatric illnesses. The Chi-square (χ^2) test was employed. The overall majority (70.0%) had a positive family history, with the IV and control groups showing the highest percentage (73.3%).

Table 10: Family history of psychiatric illnesses among the study subjects

Group	No		Yes		Total		χ^2	p-value
	N	%	N	%	N	%		
Control	8	26.7	22	73.3	30	100		
IM	11	36.6	19	63.4	30	100	0.95	0.62
IV	8	26.7	22	73.3	30	100		
Total	27	30.0	63	70.0	90	100		

Figure 11: Family history of psychiatric illnesses among the study subjects.



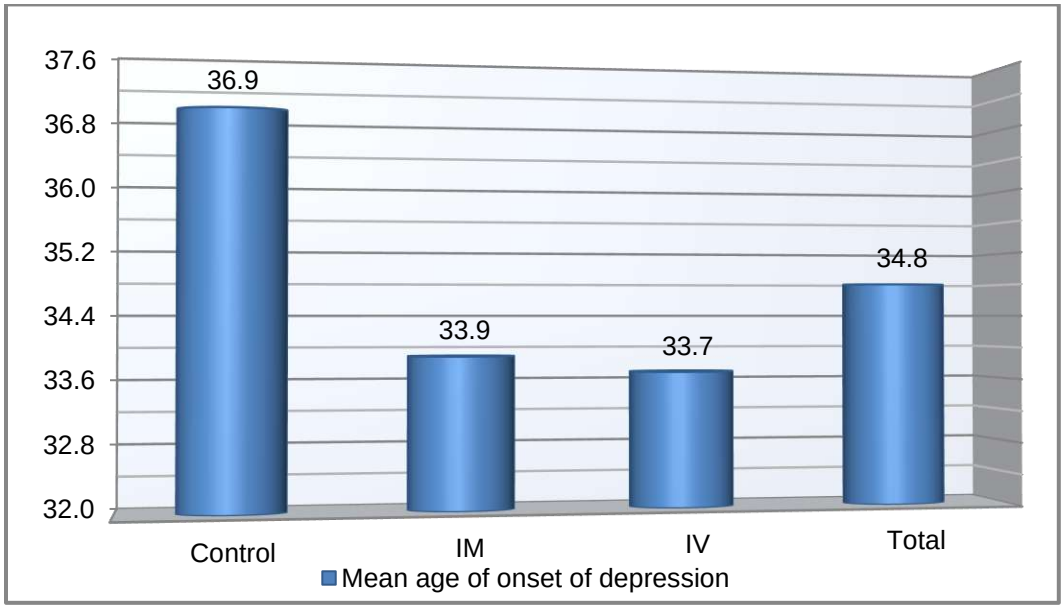
The overall majority (70.0%) had a positive family history, while 30.0% had a negative family history. The IV and control groups had the highest percentage of positive family history (73.3%), while the IM group showed 63.3% positive family history.

Table 11: Presents the distribution of patients by the mean age of onset of depression (first episode in years) and standard deviation. Among 90 patients, the mean age of onset was 34.8 years with a standard deviation of 5.4. The IV and IM groups had slightly lower mean ages of onset compared to the Control group, which had the highest mean age of onset (36.9) and standard deviation (5.7).

Table 11: Mean age of onset of depression (first episode in years) among the study subjects

Group	Mean (in years)	SD
Control	36.9	5.7
IM	33.9	5.5
IV	33.7	4.7
Total	34.8	5.4

Figure 12: Mean age of onset of depression (first episode in years) among the study subjects.



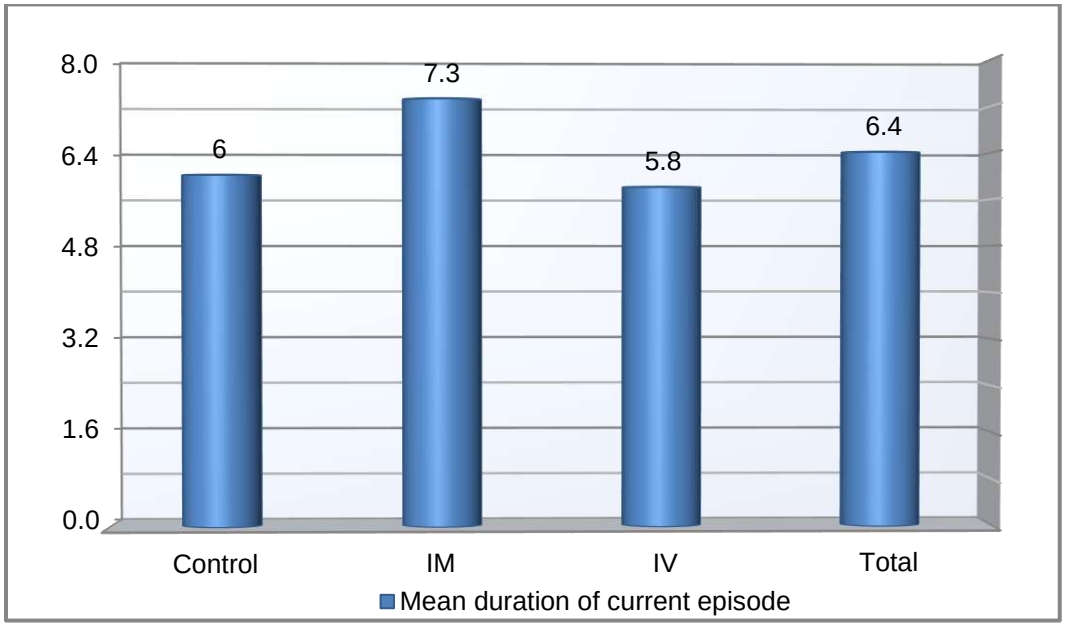
The control group had the highest mean age of onset (36.9 years), followed by the IM group (33.9 years) and the IV group (33.7 years).

Table 12 presents the distribution of patients by the mean duration of the current episode of depression in months. Among 90 patients, the mean duration was 6.4 months with a standard deviation of 2.4. The IM group had the longest mean duration, followed by the Control group, while the IV group had the shortest mean duration.

Table 12: Mean duration of current episode (months) among the study subjects

Group	Mean (in months)	SD
Control	6.0	1.9
IM	7.3	2.2
IV	5.8	2.8
Total	6.3	2.4

Figure 13: Mean duration of the current episode of depression (in months) among the study subjects.



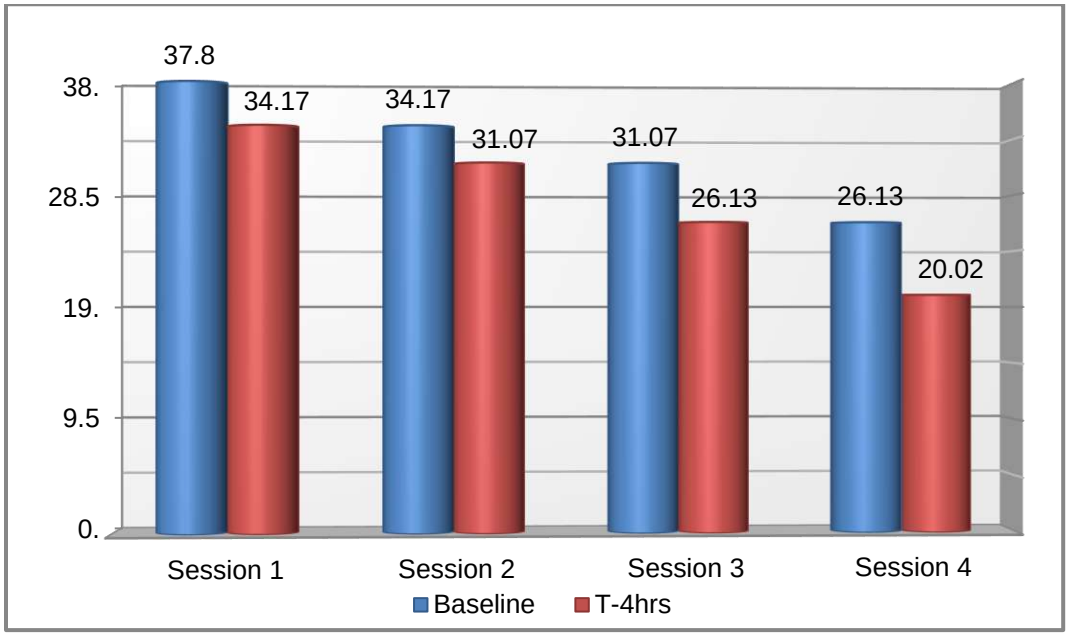
The IM group had the longest mean duration of the current episode of depression (7.3 months), followed by the control group (6.0 months), and the IV group (5.8 months), which had the shortest mean duration.

Table 13 compares MADRS scores between baseline and T-4 hours post-ketamine across four intramuscular sessions in the IM group. Each session (1 to 4) includes the mean (M) and standard deviation (SD) of MADRS scores at baseline and T-4 hours. There is a noticeable decrease in mean values at T-4 hours across all sessions. Paired t-tests show significant differences between baseline and T-4-hour values for each session, indicating a consistent and statistically significant reduction over time.

Table 13: Comparison of MADRS score in intramuscular group

Session	Baseline		T-4hrs		t-value	p-value
	Mean	SD	Mean	SD		
1	37.80	6.11	34.17	6.03	3.28	**0.041**
2	34.17	5.76	31.07	5.63	3.49	**0.046**
3	31.07	5.63	26.13	5.14	5.00	**0.023**
4	26.13	5.14	20.02	4.54	6.84	**0.009**

Figure 14: Comparison of MADRS score in intramuscular group.



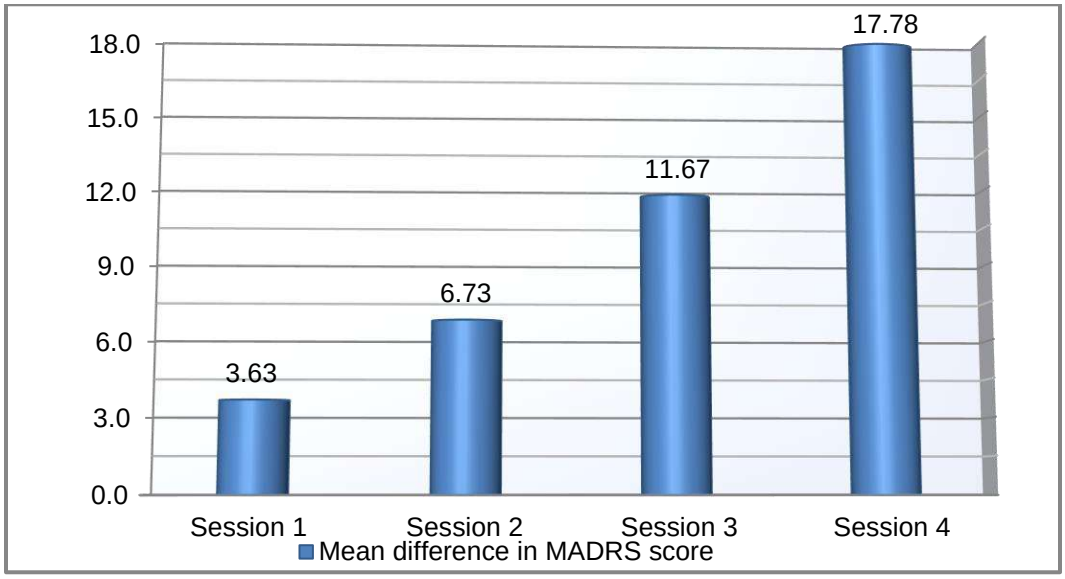
Blue series bar represents the MADRS score before ketamine and red series bar represents the MADRS score after ketamine.

Table 14 summarizes paired t-test results across four sessions, assessing mean differences between baseline and post-ketamine MADRS measurements. All sessions show highly significant mean differences, with the magnitude of the mean difference and t-values increasing across sessions.

Table 14: Mean difference in MADRS score from baseline to post-ketamine injection in each session in intramuscular group

Session	Mean Difference	SD	t-value	p-value
Session 1	3.63	1.04	20.11	**<0.001**
Session 2	6.73	1.35	28.88	**<0.001**
Session 3	11.67	2.43	27.72	**<0.001**
Session 4	17.78	2.71	37.90	**<0.001**

Figure 15: Mean difference in MADRS score from baseline to post-ketamine injection in each session in intramuscular group.



It shows a clear trend of increasing mean differences in MADRS scores from baseline to post-ketamine measurements across the four sessions. The highest mean difference is observed in Session 4 (17.78), suggesting the most significant improvement in depression symptoms

Table 15 presents the mean and percentage reduction in MADRS scores following intramuscular ketamine sessions. The mean reduction from baseline to T-4 hours in session 4 is 17.78 units, representing a 47.04% decrease relative to the baseline MADRS score.

Table 15: Percentage reduction in MADRS score from baseline till last infusion session in intramuscular group

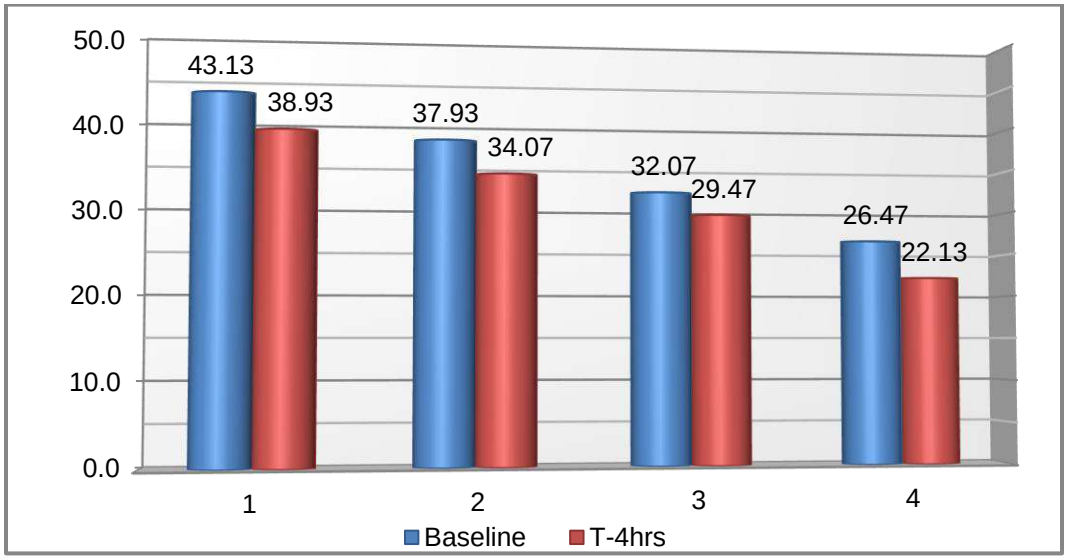
Mean Reduction	Percentage Reduction
17.78	**47.04%**

Table 16 compares MADRS scores between baseline and T-4 hours post-ketamine across four infusion sessions in the IV group. Each session (1 to 4) includes the mean (M) and standard deviation (SD) at baseline and T-4 hours. There is a noticeable decrease in mean values at T-4 hours across all sessions. Paired t-tests reveal significant differences between baseline and T-4-hour values for each session, indicating a consistent and statistically significant reduction over time.

Table 16: Comparison of MADRS score in intravenous group

Infusion Session	Baseline		T-4hrs		t-value	p-value
	Mean	SD	Mean	SD		
1	43.13	4.91	38.93	5.01	3.28	**0.032**
2	37.93	5.01	34.07	4.84	3.04	**0.03**
3	32.07	4.84	29.47	4.01	5.00	**0.025**
4	26.47	4.01	22.13	3.68	6.84	**0.008**

Figure 16: Comparison of MADRS score in intravenous group.



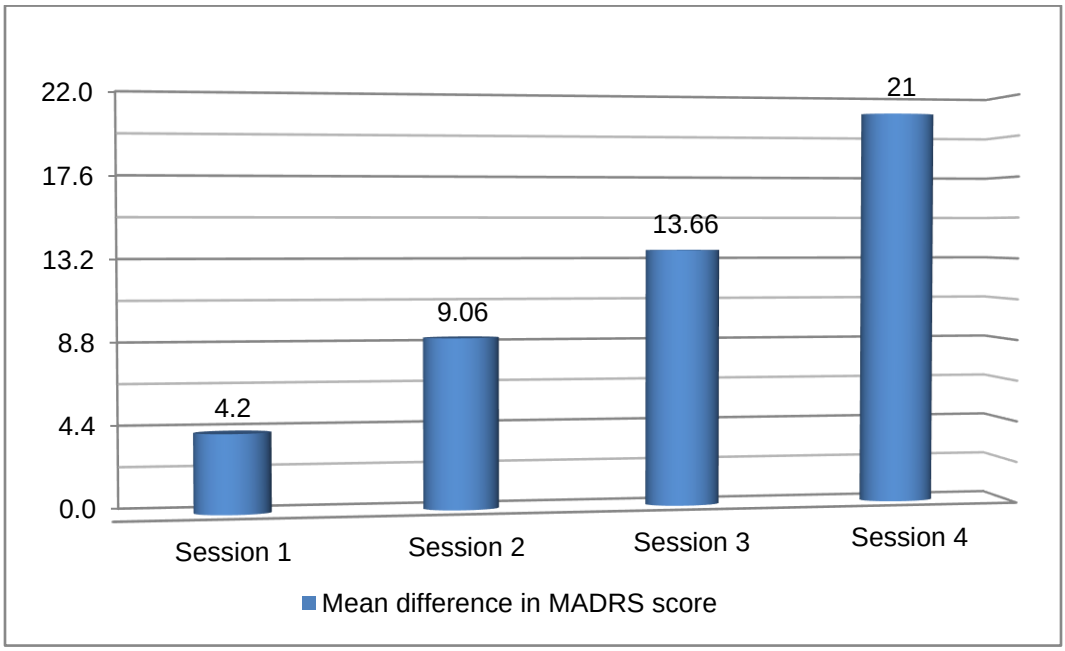
Blue series bar represents the MADRS score before ketamine and red series bar represents the MADRS score after ketamine.

Table 17 summarizes paired t-test results across four sessions, comparing mean differences between baseline and post-ketamine MADRS measurements. For each session, the mean difference, standard deviation (SD) of differences, t-value, and p-value are provided. All sessions show a significant reduction in MADRS scores from baseline to post-infusion, with p-values indicating statistical significance ($p < 0.05$).

Table 17: Mean difference in MADRS score from baseline to post-ketamine infusion in each session in intravenous group

Session	**Mean Difference**	**SD**	**t-value**	**p-value**
Session 1	4.2	1.17	19.59	**<0.001**
Session 2	9.06	1.43	34.57	**<0.001**
Session 3	13.66	3.02	24.79	**<0.001**
Session 4	21.00	3.78	30.31	**<0.001**

Figure 17: Mean difference in MADRS score from baseline to post-ketamine injection in each session in intravenous group.



It shows a clear trend of increasing mean differences in MADRS scores from baseline to post-ketamine measurements across the four sessions. The highest mean difference is observed in Session 4 (21.00), suggesting the most significant improvement in depression symptoms.

Table 18 presents the mean and percentage reduction in MADRS scores following intravenous ketamine sessions. The mean reduction from baseline to T-4 hours in session 4 is 21 units, representing a 48.69% decrease relative to the baseline MADRS score.

Table 18: Percentage reduction in MADRS score from baseline till last infusion session in intravenous group

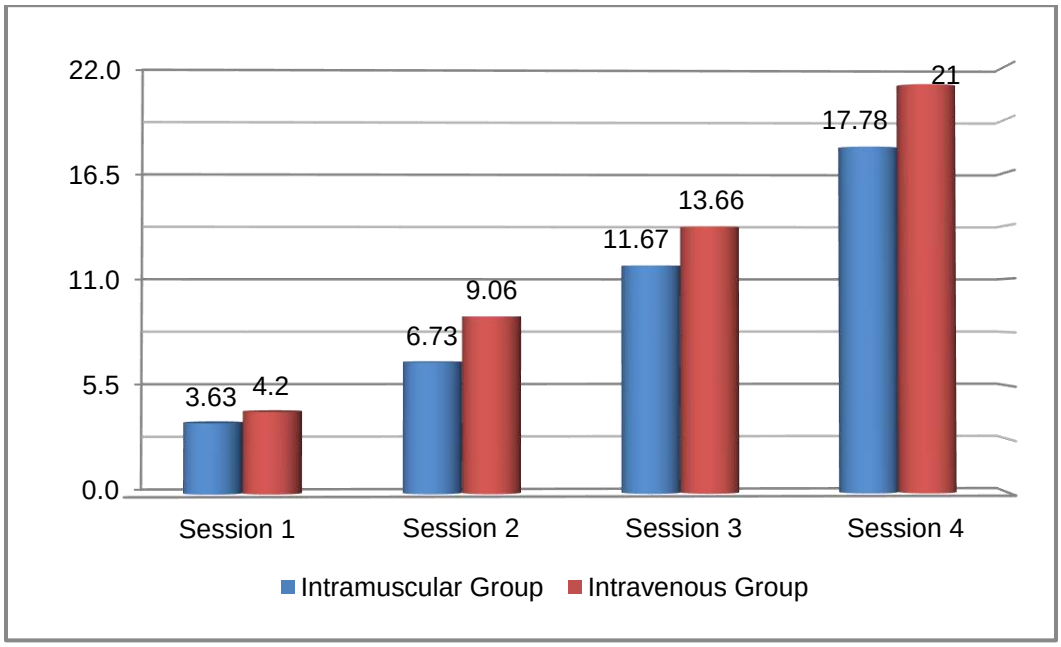
Mean Reduction	Percentage Reduction
21	**48.69%**

Table 19 presents independent samples t-test results comparing mean differences in MADRS scores between Intramuscular (IM) and Intravenous (IV) groups across four sessions (1 to 4). Only Session 2 approached statistical significance, indicating a larger mean difference in the IV group compared to the IM group. Other sessions did not show statistically significant differences.

Table 19: Comparison of Mean difference in MADRS score from baseline to post-ketamine session between intramuscular and intravenous group.

Session	**Intramuscular Group**		**Intravenous Group**		**t-value**	**p-value**
	Mean Difference	**SD**	**Mean Difference**	**SD**		
Session 1	3.63	1.04	4.2	1.17	-1.26	0.11
Session 2	6.73	1.35	9.06	1.43	-4.11	0.08
Session 3	11.67	2.43	13.66	3.02	-1.78	0.10
Session 4	17.78	2.71	21	3.78	-2.08	0.06

Figure 18: Comparison of the mean difference in MADRS scores from baseline to post-ketamine session between the intramuscular and intravenous groups.



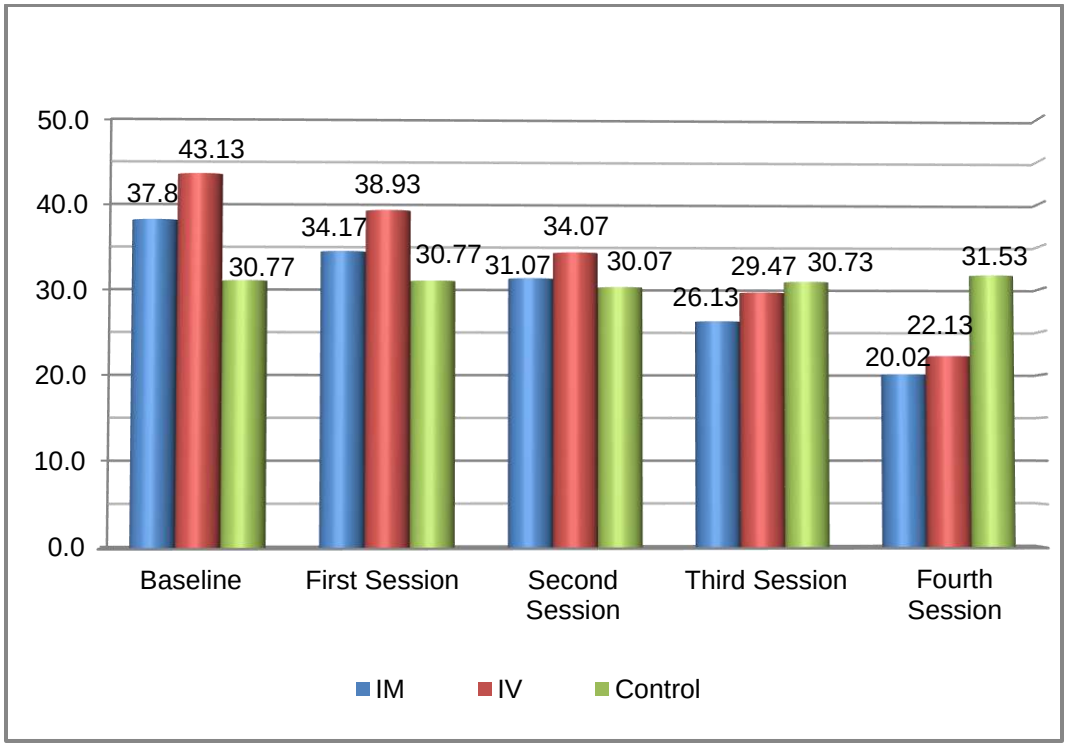
The blue bars represent the mean difference in MADRS scores for the intramuscular group, while the red bars represent the mean difference in MADRS scores for the intravenous group across all four sessions.

Table 20 presents the statistical analysis of mean values and standard deviations for Intramuscular (IM), Intravenous (IV), and Control groups across five intervals (Baseline and four sessions). For each interval, the F-statistic and p-value from a one-way ANOVA assess the significance of differences among group means. Significant differences among IM, IV, and Control groups are indicated by F-statistics and p-values (all < 0.05), confirming the differences are unlikely due to chance.

Table 20: Comparison of MADRS score in intramuscular group vs intravenous vs control

Intervals	**IM**		**IV**		**Control**		**F-statistics**	**p-value**
	Mean	**SD**	**Mean**	**SD**				
Baseline	37.80	6.11	43.13	4.91	30.77	3.83	45.09	**0.001**
First Session	34.17	6.03	38.93	5.01	30.77	3.83	19.89	**0.003**
Second Session	31.07	5.63	34.07	4.84	30.07	3.76	5.63	**0.04**
Third Session	26.13	5.14	29.47	4.01	30.73	3.83	9.96	**0.031**
Fourth Session	20.02	4.54	22.13	3.68	31.53	3.94	68.9	**0.002**

Figure 19: Comparison of MADRS score in intramuscular group vs intravenous vs control.



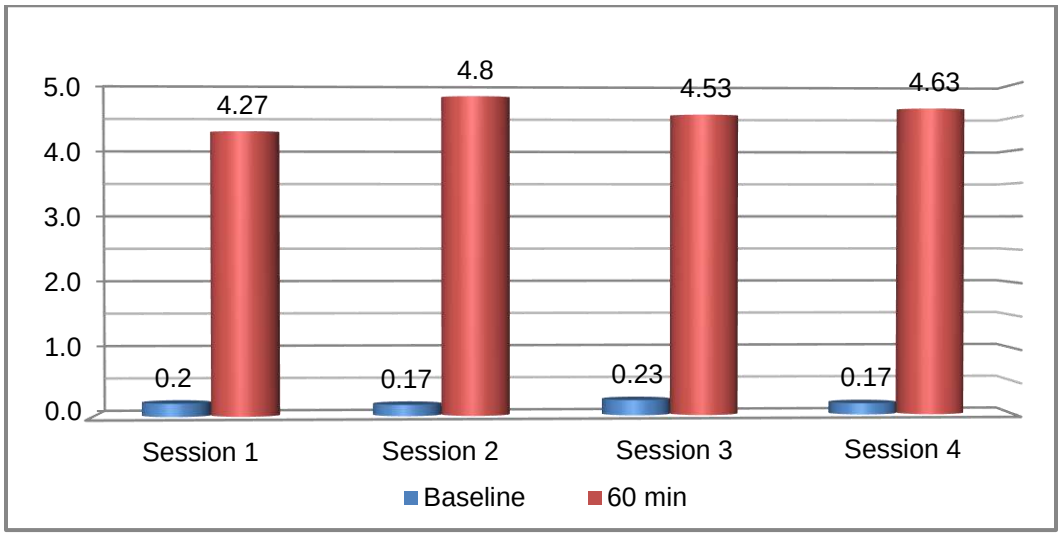
The blue bars represents the mean of MADRS score in intramuscular group, red bars represents the mean of MADRS score in intravenous group and green bars represents the mean of MADRS score in control group.

Table 21 Presents paired t-test results comparing baseline and 60-minute post-ketamine CADSS measurements across four sessions. For each session, the table includes means, standard deviations, the standard deviation of differences, t-values, and p-values. The analysis shows substantial increases in mean values from baseline to 60 minutes post-ketamine in all sessions. The high t-values and low p-values (all < 0.05) indicate statistically significant differences.

Table 21: Comparison of CADSS in intramuscular group

Session	Baseline		60 min		t- value	p-value
	Mean	SD	Mean	SD		
1	0.20	0.41	4.27	1.78	17.26	**0.001**
2	0.17	0.38	4.80	1.52	22.89	**0.001**
3	0.23	0.43	4.53	2.27	14.42	**0.001**
4	0.17	0.38	4.63	1.81	18.68	**0.001**

Figure 20: The comparison of CADSS scores in the intramuscular group.



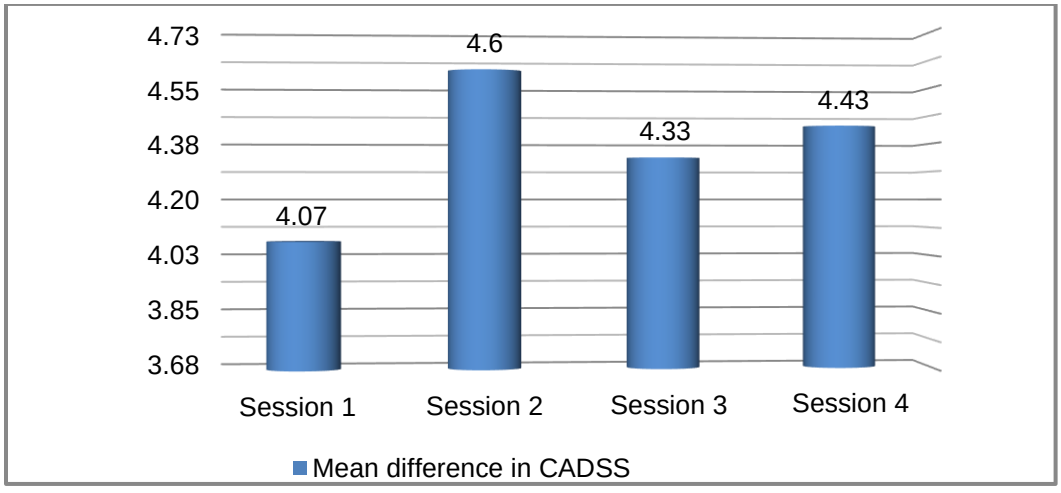
The blue bars represent the mean CADSS scores before administering ketamine, and the red bars represent the mean CADSS scores 60 minutes post-ketamine.

Table 22 presents paired t-test results comparing baseline and post-ketamine CADSS scores across four sessions. Session 1 showed a mean difference of 4.07 units with a t-value of 18.12 ($p < 0.001$). Session 2 had a mean difference of 4.60 units with a t-value of 19.10 ($p < 0.001$). In Session 3, the mean difference was 4.33 units with a t-value of 18.23 ($p < 0.001$). Session 4 showed a mean difference of 4.43 units with a t-value of 13.94 ($p < 0.001$). All sessions indicated highly significant differences.

Table 22: Mean difference in CADSS from baseline to post-ketamine in each session in intramuscular group

Session	Mean Difference	SD	t-value	p-value
Session 1	4.07	1.23	18.12	**<0.001**
Session 2	4.60	1.32	19.10	**<0.001**
Session 3	4.33	1.30	18.23	**<0.001**
Session 4	4.43	1.74	13.94	**<0.001**

Figure 21:The mean difference in CADSS scores from baseline to post-ketamine in each session for the intramuscular group.



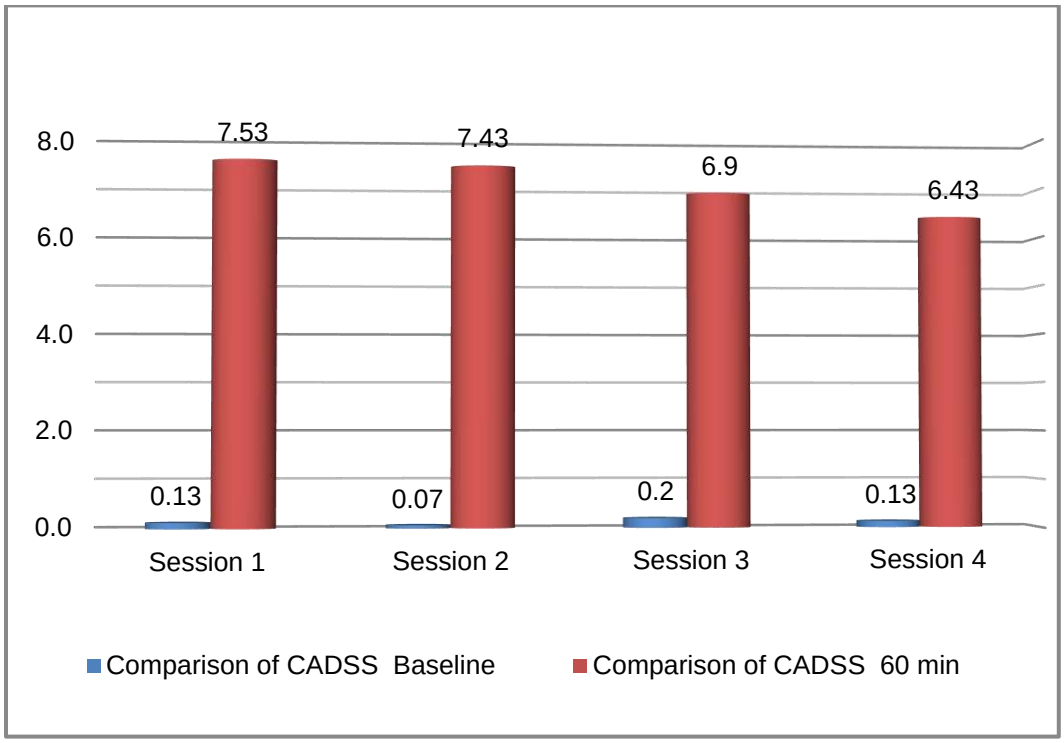
Session 2 shows the highest mean difference of 4.60, followed by Session 4 with a mean difference of 4.43.

Table 23 presents paired t-test results comparing baseline and post-ketamine CADSS measurements across four sessions. In Session 1, the mean increased from 0.13 (SD = 0.35) to 7.53 (SD = 2.58) with a t-value of 15.55 ($p < 0.01$). Session 2 saw an increase from 0.07 (SD = 0.25) to 7.43 (SD = 2.24) with a t-value of 44.89 ($p < 0.01$). In Session 3, the mean rose from 0.20 (SD = 0.41) to 6.90 (SD = 1.88) with a t-value of 19.09 ($p < 0.01$). Session 4 had a baseline mean of 0.13 (SD = 0.35), which increased to 6.43 (SD = 1.79) with a t-value of 18.91 ($p < 0.01$). All sessions showed highly significant differences.

Table 23: Comparison of CADSS in intravenous group

Infusion Session	**Baseline**		**60 min**		**t-value**	**p-value**
	Mean	**SD**	**Mean**	**SD**		
1	0.13	0.35	7.53	2.58	15.55	**<0.01**
2	0.07	0.25	7.43	2.24	44.89	**<0.01**
3	0.20	0.41	6.90	1.88	19.09	**<0.01**
4	0.13	0.35	6.43	1.79	18.91	**<0.01**

Figure 22: The comparison of CADSS scores in the intravenous group.



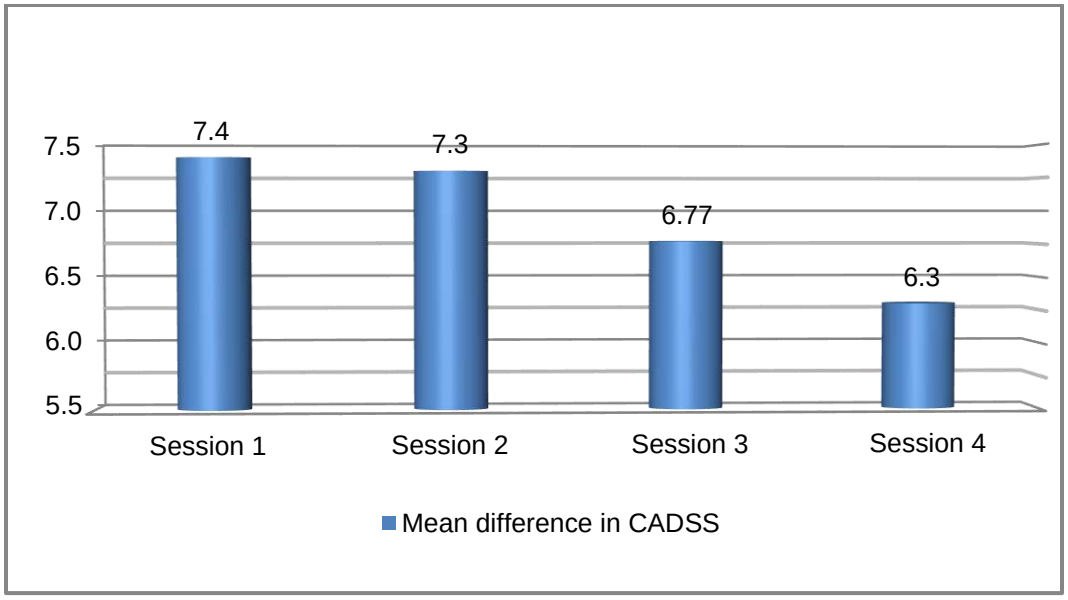
The blue bars represent the mean CADSS scores before administering ketamine, and the red bars represent the mean CADSS scores 60 minutes post-ketamine.

Table 24 presents paired t-test results comparing baseline and post-ketamine CADSS measurements across four sessions. Session 1 showed a mean difference of 7.40 units (SD = 2.14) with a t-value of 18.95 ($p < 0.001$). Session 2 had a mean difference of 7.30 units (SD = 2.20) with a t-value of 18.20 ($p < 0.001$). In Session 3, the mean difference was 6.77 units (SD = 1.92) with a t-value of 19.37 ($p < 0.001$). Session 4 showed a mean difference of 6.30 units (SD = 1.72) with a t-value of 20.13 ($p < 0.001$). All sessions indicated highly significant differences.

Table 24: Mean difference in CADSS from baseline to post-ketamine in each session in intravenous group

Session	Mean Difference	SD	t-value	p-value
Session 1	7.40	2.14	18.95	**< 0.001**
Session 2	7.30	2.20	18.20	**< 0.001**
Session 3	6.77	1.92	19.37	**< 0.001**
Session 4	6.30	1.72	20.13	**< 0.001**

Figure 23: The mean difference in CADSS scores from baseline to post-ketamine in each session for the intravenous group.



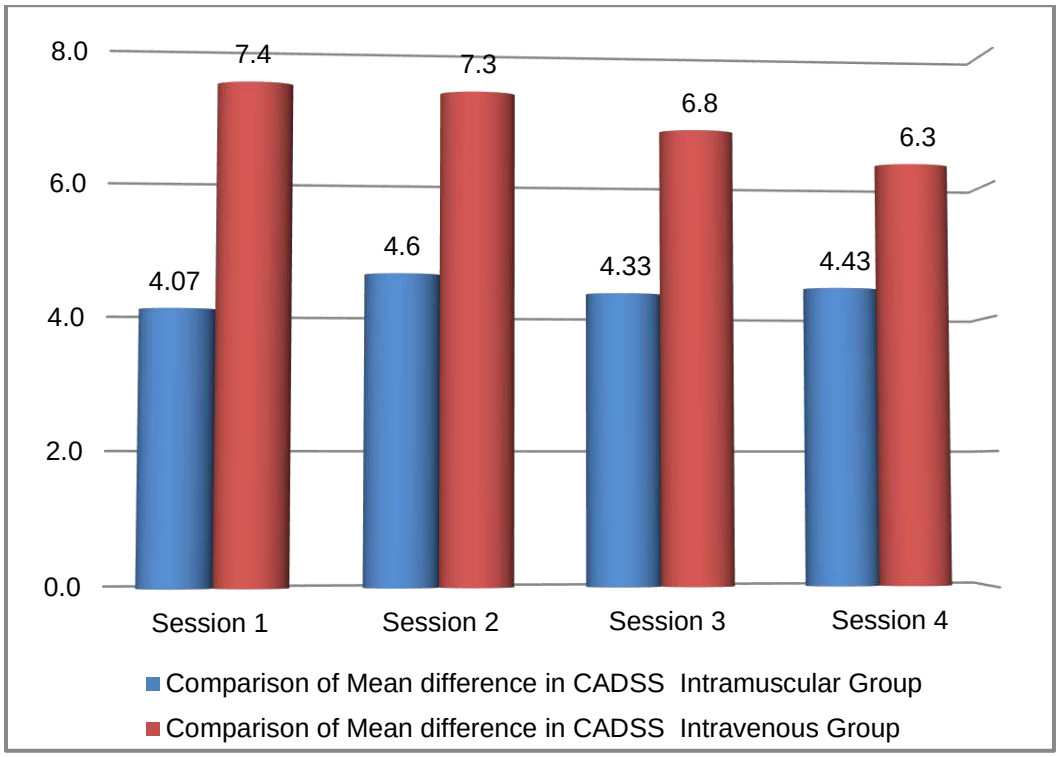
Session 1 shows the highest mean difference of 7.40, followed by Session 2 with a mean difference of 7.30, Session 3 with a mean difference of 6.8, and Session 4 with a mean difference of 6.3.

Table 25 presents independent samples t-test results comparing mean differences in CADSS scores between Intramuscular (IM) and Intravenous (IV) groups across four sessions. In Session 1, the mean differences were 4.07 (SD = 1.23) for IM and 7.40 (SD = 2.14) for IV, with a t-value of -7.37 (p = 0.001). Session 2 showed mean differences of 4.60 (SD = 1.32) for IM and 7.30 (SD = 2.20) for IV, with a t-value of -5.77 (p = 0.001). In Session 3, the mean differences were 4.33 (SD = 1.30) for IM and 6.77 (SD = 1.92) for IV, yielding a t-value of -5.83 (p = 0.004). Session 4 had mean differences of 4.43 (SD = 1.74) for IM and 6.30 (SD = 1.72) for IV, with a t-value of -4.18 (p = 0.007). All sessions indicated significant differences between the groups.

Table 25 : Comparison of Mean difference in CADSS from baseline to post-ketamine in each session between intramuscular and intravenous group

Session	**Intramuscular Group**		**Intravenous Group**		**t-value**	**p-value**
	Mean Difference	**SD**	**Mean Difference**	**SD**		
Session 1	4.07	1.23	7.40	2.14	-7.37	**0.001**
Session 2	4.60	1.32	7.30	2.20	-5.77	**0.001**
Session 3	4.33	1.30	6.77	1.92	-5.83	**0.004**
Session 4	4.43	1.74	6.30	1.72	-4.18	**0.007**

Figure 24: The Comparison of Mean difference in CADSS from baseline to post-ketamine in each session between intramuscular and intravenous group.



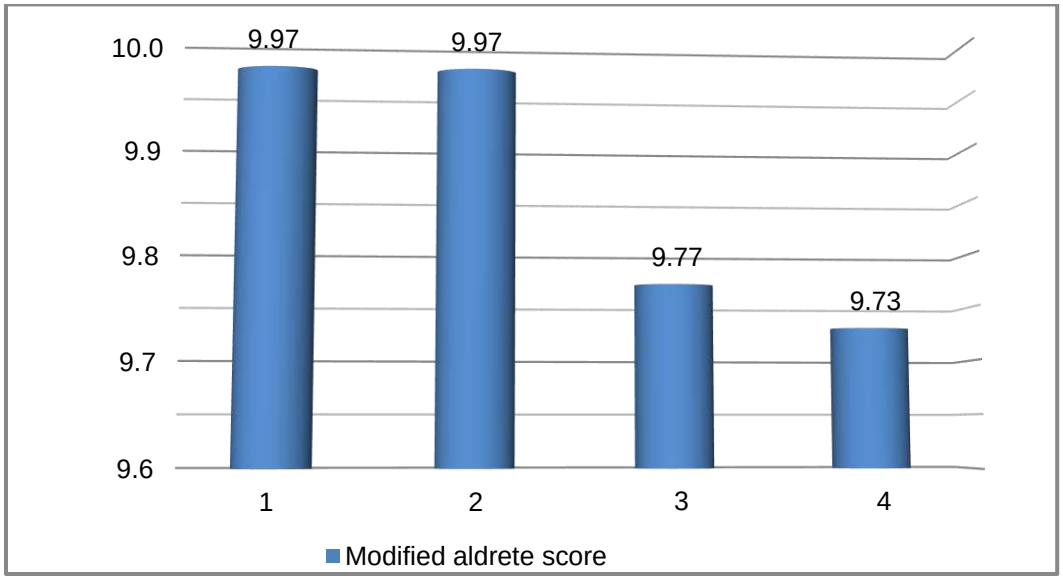
The blue bars represents the mean difference in CADSS in intramuscular group while the red bars represents the mean difference in CADSS in intravenous group.

Table 26 presents the mean and standard deviation (SD) of a measurement across four sessions. In Sessions 1 and 2, the mean is 9.97 (SD = 0.18). In Session 3, the mean decreases to 9.77 (SD = 0.43), and in Session 4, it further decreases to 9.73 (SD = 0.45). There is a slight downward trend in mean values from Session 1 to Session 4, with increasing variability.

Table 26: Modified aldrete score in intramuscular group

Session	Mean	SD
1	9.97	.18
2	9.97	.18
3	9.77	.43
4	9.73	.45

Figure 25: The Modified Aldrete score in the intramuscular group.



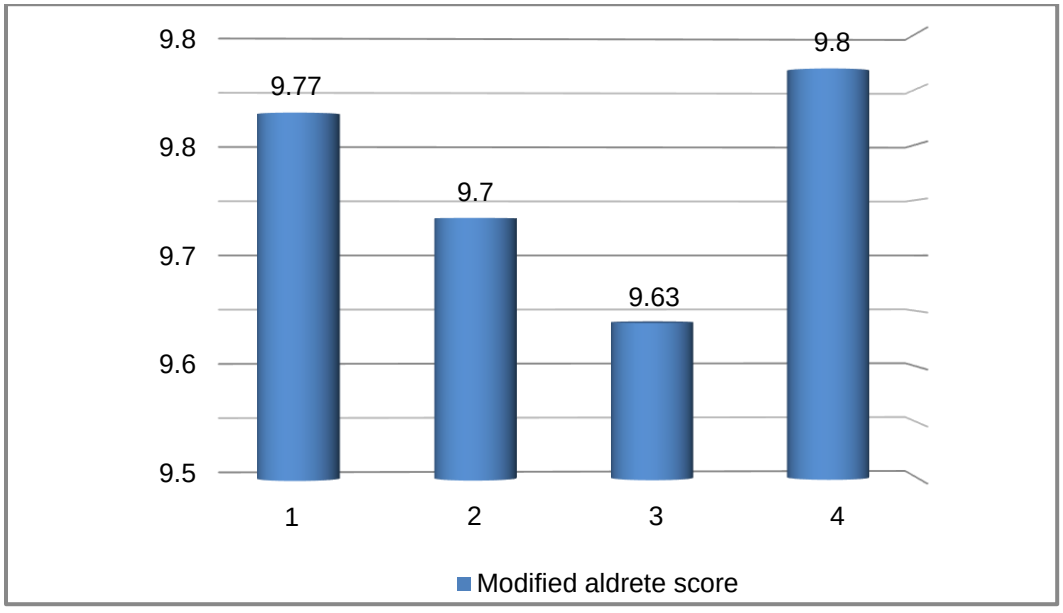
Sessions 1 and 2 show the highest mean Aldrete score (9.97), followed by Session 3 (9.77) and Session 4 (9.73).

Table 27 summarizes a study measuring a specific variable across four infusion sessions. The mean values show a slight decrease from Session 1 (9.77, SD = 0.43) to Session 3 (9.63, SD=0.49), followed by an increase in Session 4 (9.80, SD = 0.41). The standard deviations remain relatively consistent, indicating stable measurement precision across sessions.

Table 27: Modified aldrete score in intravenous group

Infusion Session	Mean	SD
1	9.77	.43
2	9.70	.47
3	9.63	.49
4	9.80	.41

Figure 26 : The Modified Aldrete score in the intravenous group.



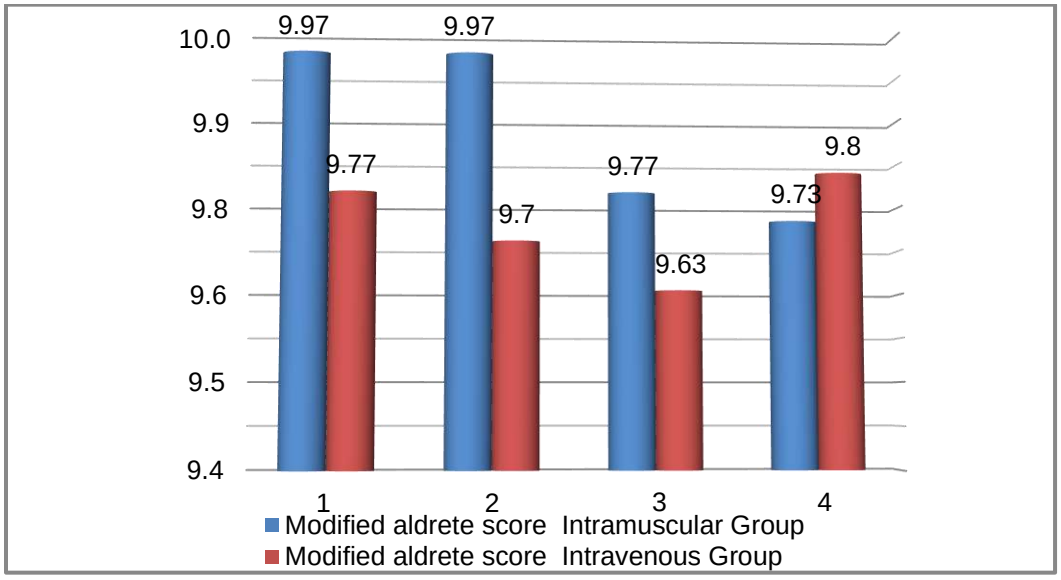
Session 4 has the highest mean score of 9.8, followed by Session 1 with a mean of 9.77, Session 2 with a mean of 9.70, and Session 3 with a mean of 9.63.

Table 28 presents the results of independent t-tests comparing the Modified Aldrete scores between the intramuscular and intravenous groups across four sessions. Significant mean differences were observed in Session 1 (t=2.35, p=0.024) and Session 2 (t=2.93, p=0.006). However, no significant differences were found in Session 3 (t=1.18, p=0.243) and Session 4 (t=-0.63, p=0.532).

Table 28: Comparison of Modified aldrete score between intramuscular and intravenous group

Session	Intramuscular Group		Intravenous Group		t-value	p-value
	Mean	SD	Mean	SD		
1	9.97	.18	9.77	.43	2.35	0.024
2	9.97	.18	9.70	.47	2.93	**0.006**
3	9.77	.43	9.63	.49	1.18	0.243
4	9.73	.45	9.80	.41	-0.63	0.532

Figure 27: Comparison of Modified Aldrete scores between the intramuscular and intravenous groups.



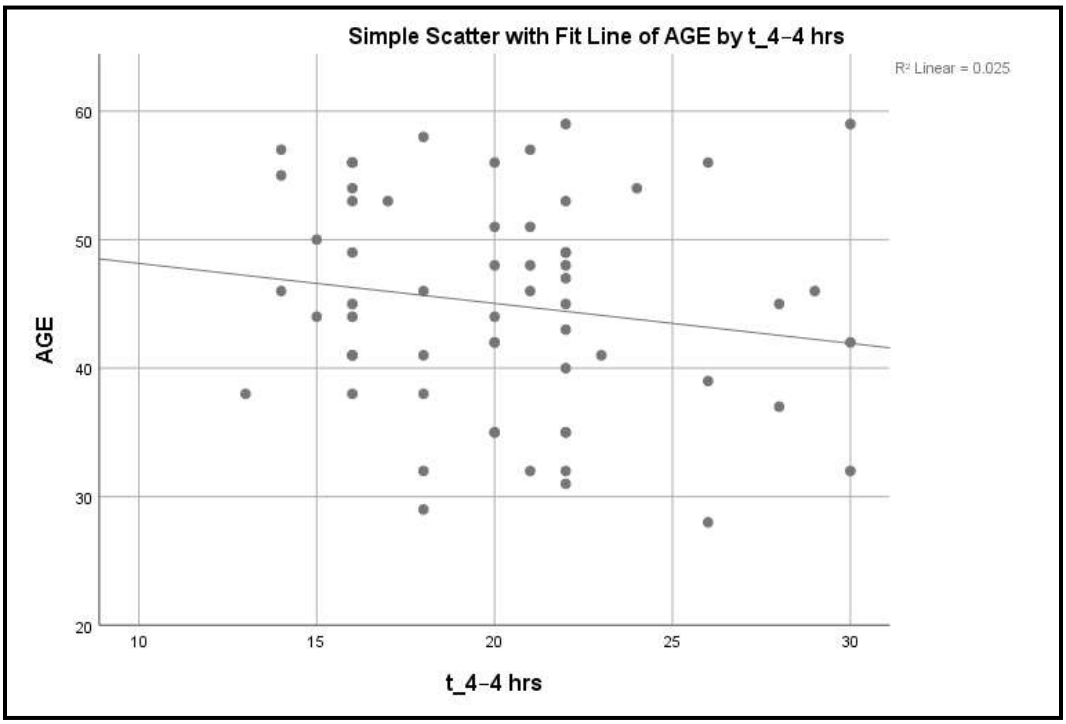
The blue bars represent the mean Modified Aldrete scores for the intramuscular group, and the red bars represent the mean Modified Aldrete scores for the intravenous group.

Table 29 presents Spearman's rank correlation results between age and the decrease in MADRS scores. The coefficient (ρ = -0.16) indicates a weak negative correlation, suggesting that as age increases, MADRS scores slightly decrease. However, the p-value of 0.22 shows this correlation is not statistically significant (α = 0.05), indicating no strong evidence of an association between age and the decrease in MADRS scores post-ketamine injection.

Table 29: Correlation between age and decrease in MADRS after giving ketamine injection

Variable 1	Variable 2	rho value	p-value
Age	MADRS	-0.16	0.22

Figure 28: The scatter plot between age and decrease in MADRS post ketamine.



It indicates that there is a weak and negative linear relationship between the variables.

Table 30 compares the mean decrease in MADRS scores post-ketamine between females and males using an independent t-test. Females have a mean of 20.19 (SD = 3.98), and males have a mean of 20.61 (SD = 4.86). The p-value of 0.78 indicates no significant difference between the groups.

Table 30: Comparison of mean decrease in MADRS scores between two genders after giving ketamine

Gender	Mean	SD	t-value	p-value
Female	20.19	3.98	-0.36	0.78
Male	20.61	4.86		

Figure 29: The mean decrease in MADRS scores between two genders after giving ketamine.

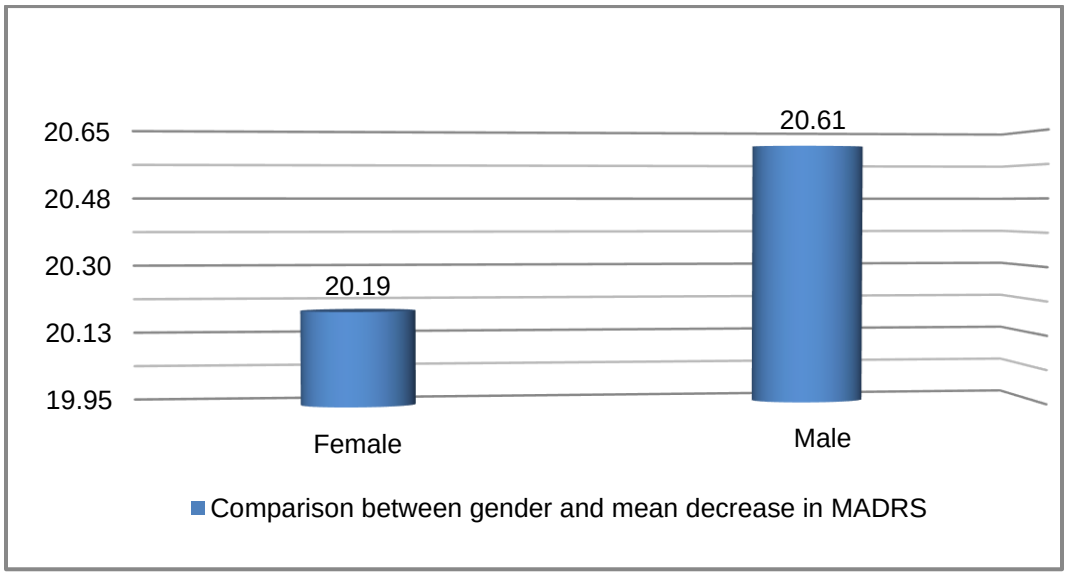
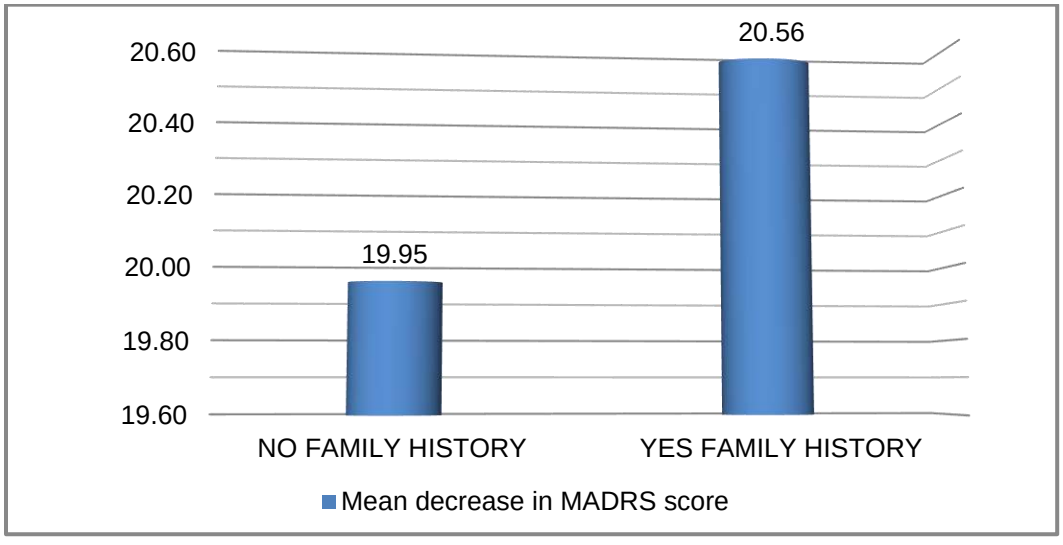


Table 31 compares mean post-ketamine scores between individuals with no family history and those with a family history using an independent samples t-test. The mean score for individuals with no family history is 19.95 (SD = 3.99), and for those with a family history, it is 20.56 (SD = 4.49). The t-value is -0.56, with a p-value of 0.6, indicating no significant difference between the groups.

Table 31: Comparison of the mean decrease in MADRS scores post-ketamine between patients with a positive family history of psychiatric illness and those with no family history of psychiatric illness.

Family History	Mean	SD	t-value	p-value
No	19.95	3.99	-0.56	0.60
Yes	20.56	4.49		

Figure 30: Compares the mean decrease in MADRS scores of patients with a family history of psychiatric illness to those with no family history after receiving ketamine.



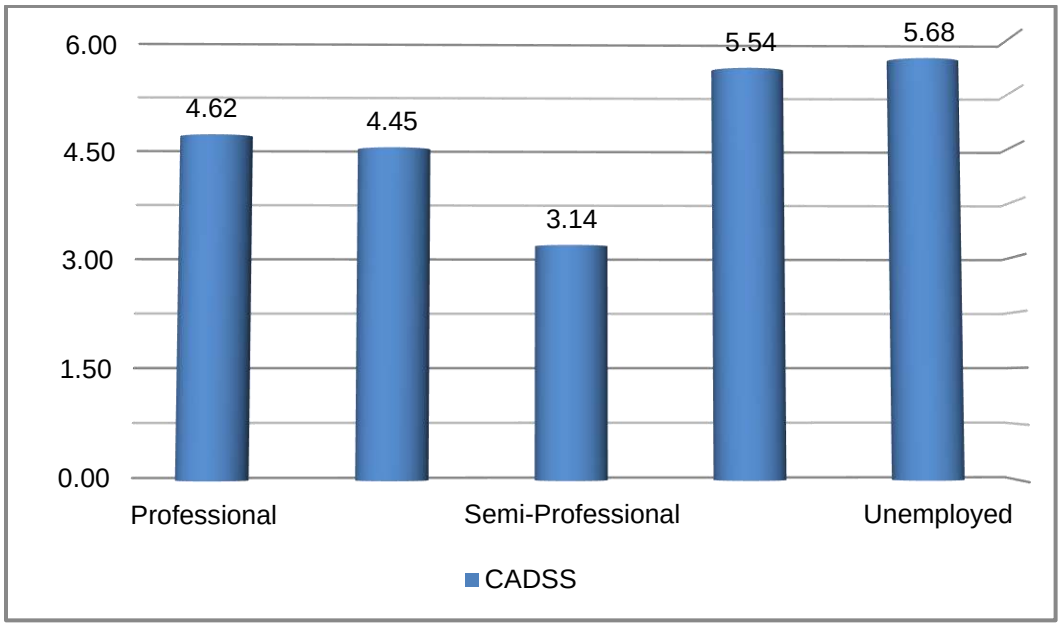
It shows that mean decrease in MADRS is higher in group having positive family history to those with no family history.

Table 32 presents descriptive statistics and ANOVA results for post-ketamine CADSS scores by occupation. Mean scores are: Professional (4.63, SD = 2.33), Semi-Skilled (4.45), Semi-Professional (3.14), Skilled (5.55, SD = 2.38), and Unemployed (5.68, SD = 1.36). The ANOVA yielded an F-value of 8.94 and a p-value of 0.11, indicating no significant differences among occupations.

Table 32: Descriptive Statistics and ANOVA Results for Post-Ketamine CADSS Scores by Occupation

Occupation	Mean	SD	F-value	p-value
Professional	4.62	2.33	8.94	0.11
Semi- Skilled	4.45	1.85		
Semi-Professional	3.14	1.07		
Skilled	5.54	2.38		
Unemployed	5.68	1.36		

Figure 31: The mean post-ketamine CADSS scores for different occupational groups. The blue bars represent the mean scores for each group, illustrating the variation in post-ketamine dissociative symptoms across occupations.



The figure shows that unemployed individuals and those in skilled occupations have higher mean CADSS scores, indicating greater post-ketamine dissociative symptoms, compared to other occupational groups. Semi-professionals have the lowest mean scores.

Table 33 Presents a comparative analysis of patients with a family history of psychiatric illnesses who received intravenous ketamine versus those in the control group. Independent t-test results showed no statistically significant differences in the mean duration of the current episode (IV ketamine: 6.6 ± 2.7 months, control: 6.1 ± 2.0 months, t=0.098, p=2.8), the mean age of onset of depression (IV ketamine: 33.67 ± 4.99 years, control: 36.70 ± 5.51 years, t=0.51, p=0.42), and the mean number of lifetime episodes (IV ketamine: 1.97 ± 0.69, control: 1.87 ± 0.68, t=0.33, p=0.56).

Table 33: Mean comparisons of patients between those receiving intravenous ketamine and control group on Duration of current episode(months), Age of onset of depression (first episode in years) and number of lifetime episodes

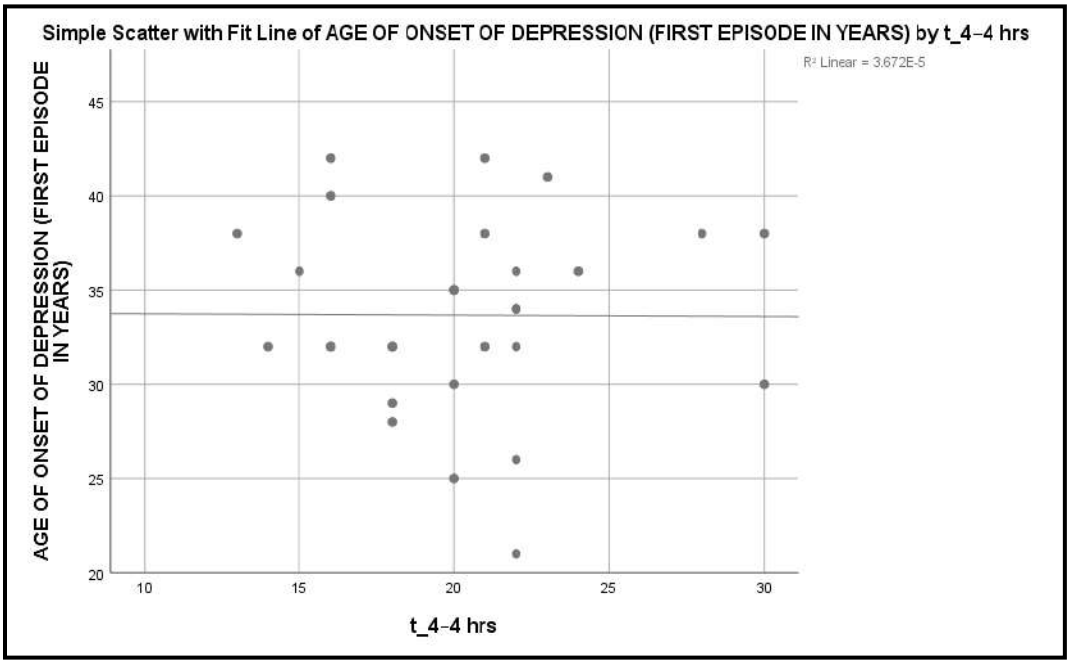
Family History	**Intravenous ketamine**	**Control**	**t-value**	**p-value**
	Mean±SD	Mean±SD		
Duration of current episode (months)	6.6±2.7	6.1±2.0	0.098	2.8
Age of onset of depression (first episode in years)	33.67±4.99	36.70±5.51	0.51	0.42
No. of lifetime episodes	1.97±0.69	1.87±0.68	0.33	0.56

Table 34 Presents Spearman's rank correlation between the decrease in MADRS after intravenous ketamine and the age of onset of depression. The correlation coefficient is 0.209, with a p-value of 0.267.

Table 34: Spearman's Rank Correlation between Decrease in MADRS Scores after Intravenous Ketamine and Age of Onset of Depression.

Variable 1	Variable 2	rho value	p-value
Decrease in MADRS after Intravenous ketamine	Age of onset of depression	0.209	0.267

Figure 32: The scatter plot between decrease in MADRS after intravenous ketamine and age of onset of depression.



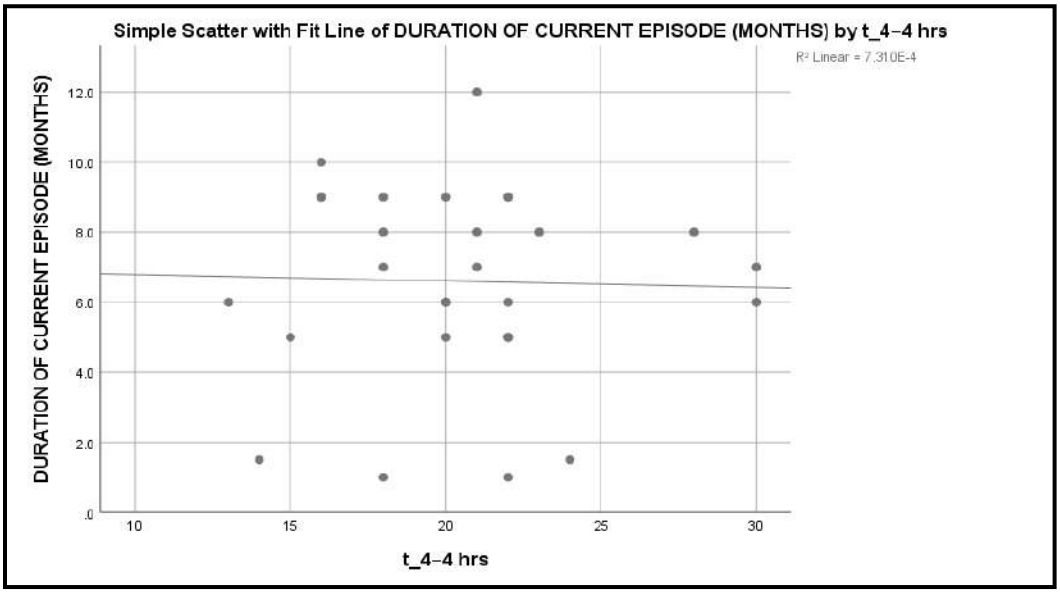
It indicates that there is no meaningful linear relationship between the variables. The trend line is almost horizontal, further indicating the lack of correlation.

Table 35 Presents Spearman's rank correlation between the decrease in MADRS after intravenous ketamine treatment and the duration of the current episode of depression. The correlation coefficient is -0.192, with a p-value of 0.311.

Table 35: Spearman's Rank Correlation between Decrease in MADRS Scores after Intravenous Ketamine and Duration of Current Episode of Depression

Variable 1	Variable 2	rho value	p-value
Decrease in MADRS after intravenous ketamine	Duration of current episode of depression	-0.192	0.311

Figure 33: The scatter plot between decrease in MADRS after intravenous ketamine treatment and the duration of the current episode of depression.



It indicates that there is no significant linear relationship between the variables. The trend line is almost horizontal, further indicating the lack of correlation.

Table 36 Presents Spearman's rank correlation between the decrease in MADRS after intravenous ketamine treatment and the number of lifetime episodes of depression. The correlation coefficient is 0.421, with a p-value of 0.21.

Table 36: Spearman's Rank Correlation between Decrease in MADRS Scores after Intravenous Ketamine and Number of Lifetime Episodes

Variable 1	**Variable 2**	**rho value**	**p-value**
Decrease in MADRS after Intravenous ketamine	No. Of lifetime episodes	0.421	0.21

Table 37 Compares patients with a family history of psychiatric illnesses who received intramuscular ketamine versus the control group using an independent t-test. The mean duration of the current episode was 7.23 ± 2.17 months for the intramuscular group and 6.10 ± 2.00 months for the control group (t=0.28, p=1.14). The mean age of onset of depression was 33.93 ± 5.55 years for the intramuscular group and 36.70 ± 5.51 years for the control group (t=0.71, p=0.13). The mean number of lifetime episodes was 2.13 ± 0.62 for the intramuscular group and 1.87 ± 0.68 for the control group (t=0.59, p=0.27).

Table 37: Mean comparisons of patients between those receiving intramuscular ketamine and control group on Duration of current episode(months), Age of onset of depression (first episode in years) and number of lifetime episodes

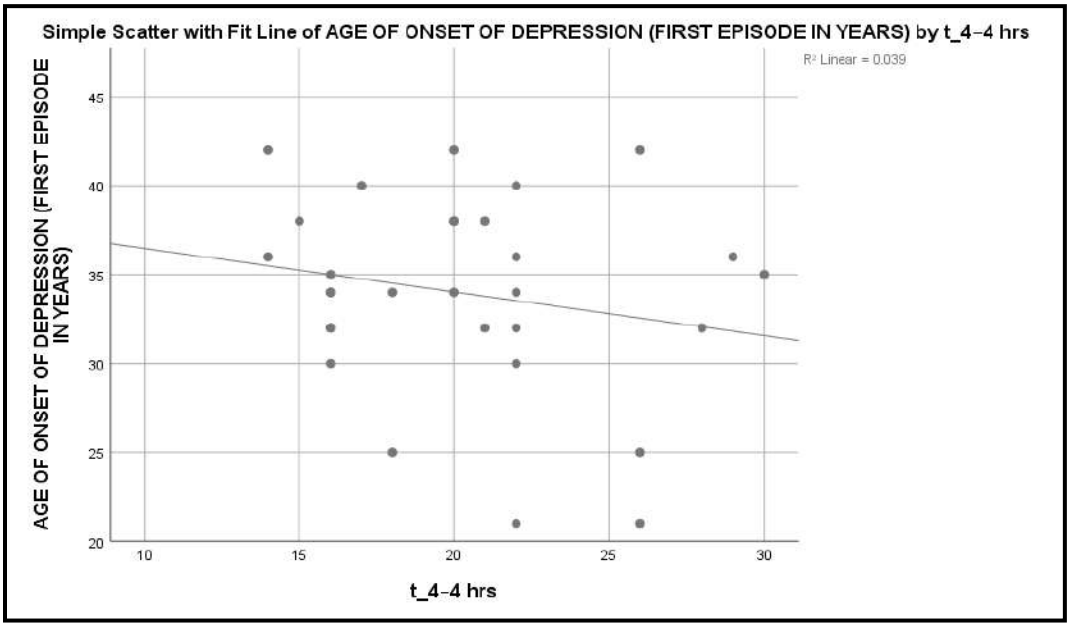
Family History	**Intramuscular ketamine**	**Control**	**t-value**	**p-value**
	Mean±SD	Mean±SD		
Duration of current episode (months)	7.23±2.17	6.10±2.00	0.28	1.14
Age of onset of depression (first episode in years)	33.93±5.55	36.70±5.51	0.71	0.13
No. of lifetime episodes	2.13±0.62	1.87±0.68	0.59	0.27

Table 38 Presents Spearman's rank correlation between the decrease in MADRS after intramuscular ketamine treatment and the age of onset of depression. The correlation coefficient is -0.198, with a p-value of 0.294.

Table 38: Spearman's Rank Correlation between Decrease in MADRS Scores after Intramuscular Ketamine and Age of Onset of Depression

Variable 1	Variable 2	rho value	p-value
Decrease in MADRS after Intramuscular ketamine	Age of onset of depression	-0.198	0.294

Figure 34: The scatter plot between decrease in MADRS after intramuscular ketamine treatment and the age of onset of depression.



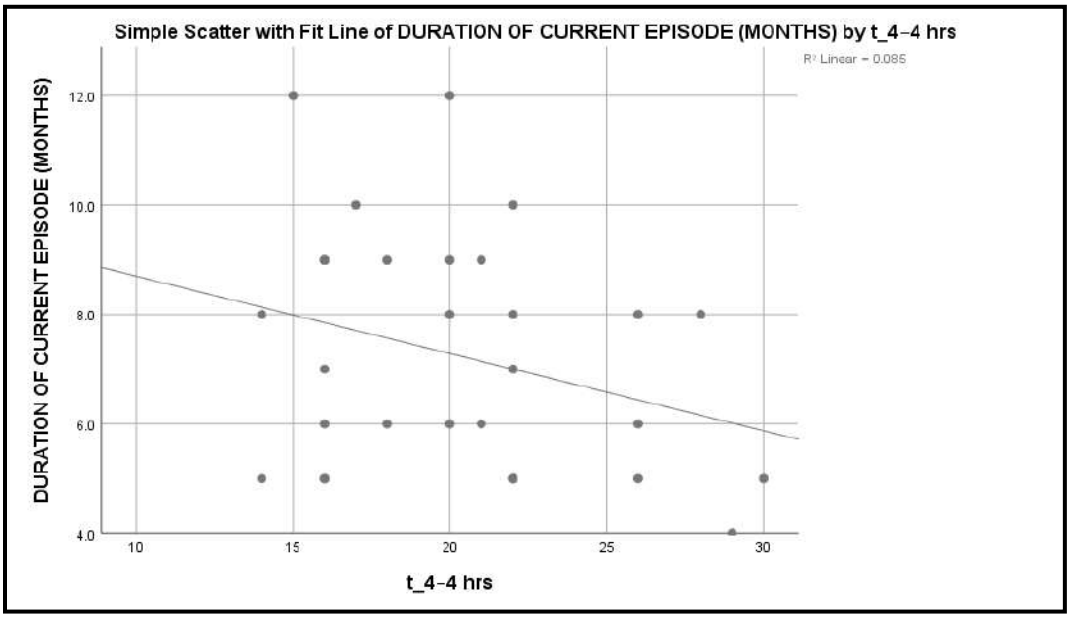
It indicates that there is a weak negative linear relationship between the variables.

Table 39 Presents Spearman's rank correlation between the decrease in MADRS after intramuscular ketamine treatment and the duration of the current episode of depression. The correlation coefficient is -0.291, with a p-value of 0.118.

Table 39: Spearman's Rank Correlation between Decrease in MADRS Scores after Intramuscular Ketamine and Duration of Current Episode of Depression

Variable 1	Variable 2	rho value	p-value
Decrease in MADRS after Intramuscular ketamine	Duration of current episode of depression	-0.291	0.118

Figure 35: The scatter plot between decrease in MADRS after intramuscular ketamine treatment and the duration of the current episode of depression.



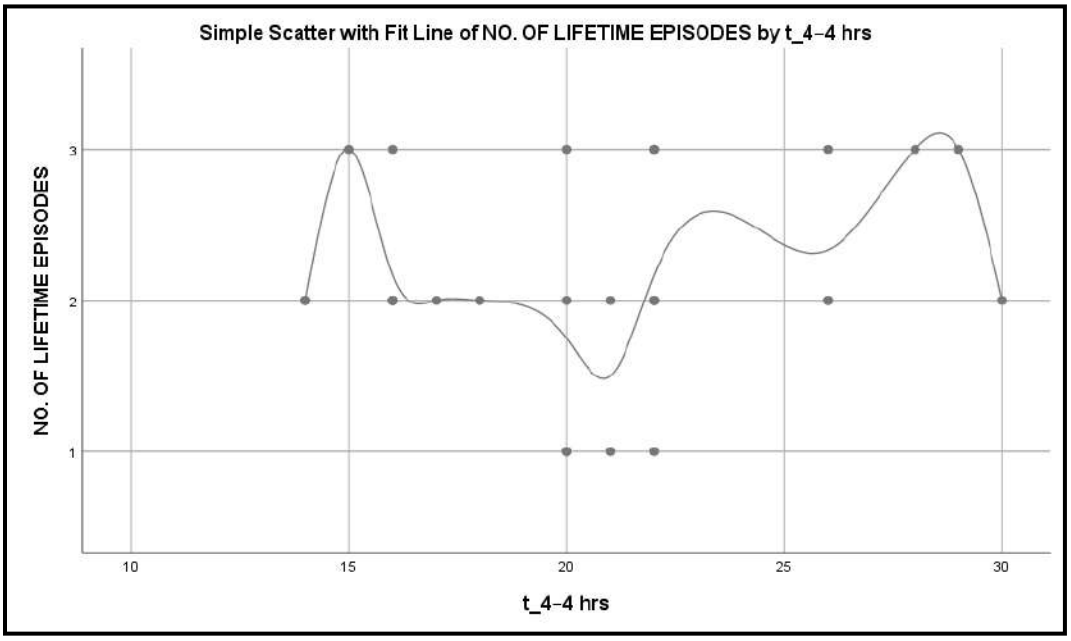
It indicates that there is a weak negative linear relationship between the variables.

Table 40 Presents Spearman's rank correlation between the decrease in MADRS after intramuscular ketamine treatment and the number of lifetime episodes of depression. The correlation coefficient is 0.140, with a p-value of 0.461.

Table 40: Spearman's Rank Correlation between Decrease in MADRS Scores after Intramuscular Ketamine and Number of Lifetime Episodes

Variable 1	Variable 2	rho value	p-value
Decrease in MADRS after Intramuscular ketamine	No. Of lifetime episodes	0.140	0.461

Figure 36: The scatter plot between decrease in MADRS after intramuscular ketamine treatment and the number of lifetime episodes of depression.



It indicates that there is a non-linear relationship between the variables.

RESULTS

Table 2 and Figure 3: The table and figure presented offer a comprehensive analysis of the distribution of male and female participants across three groups: Control, IM (Intramuscular), and IV (Intravenous), including total numbers and percentages. The Chi-square (χ^2) test was employed to assess gender distribution differences among the groups. In the Control group, there are 17 males (56.7%) and 13 females (43.3%), with a total 30 participants. The IM group comprises 12 males (40.0%) and 18 females (60.0%), with a total 30 participants. The IV group includes 9 males (30.0%) and 21 females (70.0%), with a total of 30 participants. Overall, the study involves 90 participants, with 38 males (42.2%) and 52 females (57.8%). The Chi-square value is 4.46, and the p-value is 0.11, indicating no statistically significant difference in gender distribution among the three groups. The figure visually illustrates these distributions, showing a higher number of females in both the IM and IV groups compared to males. Specifically, the IV group has the highest number of female participants and the lowest number of male participants, highlighting a notable gender distribution difference compared to the other groups. The Control group exhibits a relatively balanced gender distribution, while the IM group shows a moderate female predominance.

Table 3 and Figure 4: Present a comparative analysis of the age distribution of participants across three groups: Control, IM (Intramuscular), and IV (Intravenous), along with the Chi-square (χ^2) test value and p-value to assess the statistical significance of age distribution differences among the groups. In the 25-34 years age group, there are 5 participants (16.7%) in the Control group, 4 participants (13.3%) in the IM group, and 3 participants (10.0%) in the IV group. For the 35-44 years age group, the Control and IV groups each have 10 participants (33.3%), while the IM group has 8 participants (26.7%). In the 45-54 years age group, the Control group has 7 participants (23.3%), the IM group has 13 participants (43.3%), and the IV group has 9 participants (30.0%). For participants

aged over 54 years, the Control and IV groups each have 8 participants (26.7%), and the IM group has 5 participants (16.7%). Each group (Control, IM, IV) consists of 30 participants (33.3%). The mean age and standard deviation (SD) are 44.9 ±9.92 for the Control group, 45.17 ± 8.60 for the IM group, and 43.13 ±8.16 for the IV group. The Chi-square (χ^2) value is 3.57 with a p-value of 0.73, indicating no significant differences in age distribution among the groups. The highest percentage of participants is in the 35-44 age range for the Control and IV groups, and in the 45-54 age range for the IM group. The mean age is similar across all groups, with no significant age distribution differences as indicated by the Chi-square test (p-value = 0.73). The bar chart visually represents these findings, showing the number of participants in each age category for the Control, IM, and IV groups, with blue bars for the Control group, red bars for the IM group, and green bars for the IV group. The figure representation confirms the higher concentration of participants in the 45-54 years age range for the IM group and in the 35-44 years age range for the Control and IV groups, with the IV group having the lowest number of participants in the 25-34 years age range.

Table 4 and Figure 5: Presents a comparative analysis of the marital status (Married vs. Unmarried) of patients across three groups: Control, IM (Intramuscular), and IV (Intravenous), including the Chi-square (χ^2) test value and p-value to assess the statistical significance of marital status distribution among the groups. In the Control group, 29 patients (96.7%) are married, and 1 patient (3.3%) is unmarried. In the IM group, 28 patients (93.3%) are married, and 2 patients (6.7%) are unmarried. Similarly, in the IV group, 28 patients (93.3%) are married, and 2 patients (6.7%) are unmarried. Overall, there are 85 married patients (94.4%) and 5 unmarried patients (5.6%) out of a total of 90 patients. The Chi-square test value is 0.42, with a p-value of 0.81, indicating no statistically significant difference in marital status distribution among the groups. Most patients in all three groups are married, with the Control group having the

highest percentage of married patients. The accompanying bar chart figure illustrates the marital status distribution of patients across the three groups: Control, IM, and IV. The blue bars represent married patients, while the red bars represent unmarried patients. In the Control group, approximately 29 patients are married, and around 1 patient is unmarried. In the IM group, about 28 patients are married, and approximately 2 patients are unmarried. Similarly, in the IV group, around 28 patients are married, and approximately 2 patients are unmarried. Overall, the figure highlights that the majority of patients in all three groups are married, with very few unmarried patients in each group. The marital status distribution is similar across the Control, IM, and IV groups.

Table 5 and Figure 6: The table presents the educational level distribution of patients across three groups: Control, IM (Intramuscular), and IV (Intravenous), along with the total distribution and the results of the Chi-square (χ^2) test to assess the statistical significance of differences among the groups. In the Control group, 2 patients (6.7%) have a primary school education, 1 patient (3.3%) has a middle school education, 14 patients (46.7%) have a higher secondary school education, 10 patients (33.3%) are graduates, and 3 patients (10.0%) are postgraduates. In the IM group, 3 patients (10.0%) have a primary school education, 6 patients (20.0%) have a middle school education, 9 patients (30.0%) have a higher secondary school education, 10 patients (33.3%) are graduates, and 2 patients (6.7%) are postgraduates. In the IV group, 5 patients (16.7%) have a primary school education, 3 patients (10.0%) have a middle school education, 10 patients (33.3%) have a higher secondary school education, 11 patients (36.7%) are graduates, and 1 patient (3.3%) is a postgraduate. Overall, 10 patients (11.1%) have a primary school education, 10 patients (11.1%) have a middle school education, 33 patients (36.7%) have a higher secondary school education, 31 patients (34.4%) are graduates, and 6 patients (6.7%) are postgraduates. The Chi-square (χ^2) test value is 7.35, with a p-value of 0.48, indicating no statistically significant

differences in educational level distribution among the groups. The bar chart illustrates the educational level distribution of patients across the three groups: Control (blue bars), IM (Intramuscular, red bars), and IV (Intravenous, green bars). The educational levels are categorized into primary school, middle school, higher secondary school, graduate, and postgraduate. For primary school education, the IV group has the highest number of patients with approximately 5, followed by the IM group with around 3, and the Control group with about 2. In the middle school category, the IM group leads with 6 patients, followed by the IV group with 3, and the Control group with 1. The higher secondary school category shows the highest numbers in the Control group with approximately 14 patients, followed by the IV group with around 10, and the IM group with about 9. In the graduate category, the IV group has the highest number of patients with about 11, closely followed by the IM and Control groups, each with approximately 10 patients. The postgraduate category has the least number of patients across all groups, with the Control group having about 3, the IM group with around 2, and the IV group with only 1 patient. Overall, the chart shows that the higher secondary school and graduate categories have the highest number of patients across all groups, while the primary school and postgraduate categories have the fewest. The distribution is relatively balanced across the three groups, with slight variations in each educational category.

Table 6 and Figure 7: The table presents a comparative analysis of the occupational distribution of patients across three groups: Control, IM (Intramuscular), and IV (Intravenous), along with the total distribution and the results of the Chi-square (χ^2) test value and p-value to assess the statistical significance of differences among the groups. In the Control group, 12 patients (40.0%) are unemployed, 7 patients (23.3%) are semi-skilled, 9 patients (30.0%) are skilled, none are semi-professional, and 2 patients (6.7%) are professional. In the IM group, 11 patients (36.7%) are unemployed, 5 patients (16.7%) are semi-skilled, 4 patients (13.3%) are

skilled, 4 patients (13.3%) are semi-professional, and 6 patients (20.0%) are professional. In the IV group, 11 patients (36.7%) are unemployed, 6 patients (20.0%) are semi-skilled, 7 patients (23.3%) are skilled, 4 patients (13.3%) are semi-professional, and 2 patients (6.7%) are professional. Overall, the total distribution shows that 34 patients (37.8%) are unemployed, 18 patients (20.0%) are semi-skilled, 20 patients (22.2%) are skilled, 8 patients (8.9%) are semi-professional, and 10 patients (11.1%) are professional. The Chi-square (χ^2) test value is 9.54 with a p-value of 0.29, indicating no statistically significant differences in occupational distribution among the groups. The bar chart illustrates the occupational distribution of patients across three groups: Control (blue bars), IM (Intramuscular, red bars), and IV (Intravenous, green bars). The categories of occupation include unemployed, semi-skilled, skilled, semi-professional, and professional. Among the Control group, the largest number of patients is unemployed, followed by skilled, semi-skilled, and professional, with no semi-professional patients. In the IM group, the highest number of patients is unemployed, followed by professional, semi-skilled, semi-professional, and skilled. In the IV group, the largest number of patients is unemployed, followed by skilled, semi-skilled, semi-professional, and professional. Overall, the chart indicates that the unemployed category has the highest number of patients across all groups, while the semi-professional category has the least. The distribution across the groups shows some variation, with the Control and IV groups having a similar pattern of higher unemployment and a significant number of skilled workers, whereas the IM group shows a higher proportion of professionals.

Table 7 and Figure 8: The table and accompanying bar presents a comparative analysis of the family structure (Joint vs. Nuclear) of patients across three groups: Control, IM (Intramuscular), and IV (Intravenous), along with the Chi-square (χ^2) test value and p-value to assess the statistical significance of differences among the groups. In the Control

group, 6 patients (20.0%) come from joint families, while 24 patients (80.0%) come from nuclear families. The IM group has 3 patients (10.0%) from joint families and 27 patients (90.0%) from nuclear families. The IV group includes 6 patients (20.0%) from joint families and 24 patients (80.0%) from nuclear families. Overall, the total distribution shows 15 patients (16.7%) from joint families and 75 patients (83.3%) from nuclear families. The Chi-square (χ^2) test value is 1.44 with a p-value of 0.49, indicating no statistically significant differences in family structure distribution among the groups. Figure illustrates the family structure distribution (Joint vs. Nuclear) of patients across the three groups: Control (blue bars), IM (Intramuscular, red bars), and IV (red bars). The chart shows that in the Control group, approximately 6 patients are from joint families and 24 are from nuclear families. In the IM group, about 3 patients are from joint families and 27 are from nuclear families. In the IV group, around 6 patients are from joint families and 24 are from nuclear families. Overall, the chart indicates that the majority of patients across all groups are from nuclear families, with a smaller proportion coming from joint families. The distribution is similar across the Control, IM, and IV groups, with nuclear families being more prevalent in each group.

Table 8 and Figure 9: The table presents a comprehensive analysis of the residential distribution (Rural vs. Urban) of patients across three groups: Control, IM (Intramuscular), and IV (Intravenous), along with the Chi-square (χ^2) test value and p-value to assess the statistical significance of differences among these groups. In the Control group, 12 patients (40.0%) are from rural areas, while 18 patients (60.0%) are from urban areas. The IM group includes 6 patients (20.0%) from rural areas and 24 patients (80.0%) from urban areas. Similarly, the IV group comprises 11 patients (36.7%) from rural areas and 19 patients (63.3%) from urban areas. The overall distribution indicates that 29 patients (32.2%) are from rural areas, whereas 61 patients (67.8%) are from urban areas. The Chi-square (χ^2) test value of 3.15 with a p-value of 0.26 suggests no

statistically significant differences in residential distribution among the groups. The accompanying bar chart illustrates the residential distribution of patients across the three groups, with blue bars representing the Control group, red bars representing the IM group, and green bars representing the IV group. The chart shows that in the Control group, approximately 12 patients are from rural areas and 18 from urban areas. In the IM group, about 6 patients are from rural areas and 24 from urban areas. In the IV group, around 11 patients are from rural areas and 19 from urban areas. Overall, the chart highlights that the majority of patients across all groups are from urban areas, with a smaller proportion coming from rural areas. The distribution pattern is consistent across the Control, IM, and IV groups, indicating a higher prevalence of urban patients in each group.

Table 9 and Figure 10: The table and accompanying bar presents the distribution of participants based on the number of depressive episodes across three groups: Control, IM (Intramuscular), and IV (Intravenous). In the Control group, 8 participants (26.7%) experienced one depressive episode, 17 participants (56.7%) experienced two depressive episodes, and 5 participants (16.7%) experienced three depressive episodes. In the IM group, 6 participants (20.0%) had one depressive episode, 17 participants (56.7%) had two episodes, and 7 participants (23.3%) had three episodes. In the IV group, 8 participants (26.7%) had one episode, 16 participants (53.3%) had two episodes, and 6 participants (20.0%) had three episodes. Overall, out of 90 participants, 22 (24.4%) had one episode, 50 (55.6%) had two episodes, and 18 (20.0%) had three episodes. The Chi-square (χ^2) test value is 0.95, with a p-value of 0.62, indicating no statistically significant differences among the groups. Figure 9 illustrates these distributions, showing that the majority of patients across all groups experienced two depressive episodes, followed by one episode, and the fewest experienced three episodes. This pattern is consistent across the Control, IM, and IV groups, with more than half of

the participants in each group falling into the two-episode category. The overall trend indicates a higher prevalence of two depressive episodes among the patients.

Table 10 and Figure 11: The table presents a comparative analysis of patients with and without a family history of psychiatric illnesses across three groups: Control, IM (Intramuscular), and IV (Intravenous). In the Control group, 8 patients (26.7%) have no family history of psychiatric illnesses, while 22 patients (73.3%) have a family history. In the IM group, 11 patients (36.6%) have no family history, and 19 patients (63.4%) have a family history. In the IV group, 8 patients (26.7%) have no family history, and 22 patients (73.3%) have a family history. Overall, the total distribution shows that 27 patients (30.0%) have no family history, while 63 patients (70.0%) have a family history. The Chi-square (χ^2) test value is 0.95, with a p-value of 0.62, indicating no statistically significant differences in the distribution of family history of psychiatric illnesses among the groups.The accompanying bar chart illustrates the family history of psychiatric illnesses among patients in three groups: Control (blue bars), IM (Intramuscular, red bars), and IV (green bars). Each group is compared across two categories: patients with no family history of psychiatric illnesses and patients with a family history of psychiatric illnesses. In the Control group, approximately 8 patients have no family history of psychiatric illnesses, while around 22 patients have a family history. In the IM group, about 11 patients have no family history, and approximately 19 patients have a family history. In the IV group, around 8 patients have no family history, while about 22 patients have a family history. Overall, the chart indicates that a majority of patients in all three groups have a family history of psychiatric illnesses, with the IM group having a slightly higher number of patients with no family history compared to the Control and IV groups. The distribution is similar across the Control and IV groups, showing a higher prevalence of family history of psychiatric illnesses among the patients.

Table 11 and Figure 12: The table and accompanying bar chart present the mean age of onset of depression (in years) and the standard deviation (SD) for patients across three groups: Control, IM (Intramuscular), and IV (Intravenous), along with the overall total. The Control group has a mean age of onset of 36.9 years with an SD of 5.7, indicating that this group experiences the onset of depression at a later age compared to the other groups. The IM group shows a mean age of onset of 33.9 years with an SD of 5.5, while the IV group has the lowest mean age of onset at 33.7 years with an SD of 4.7. The overall total mean age of onset across all groups is 34.8 years with an SD of 5.4, reflecting a slightly lower mean age of onset compared to the Control group but higher than both the IM and IV groups. The bar chart visually reinforces these findings, with the tallest bar representing the Control group's mean age of onset, followed by the IM and IV groups. The overall mean age of onset bar is positioned between the Control group's higher mean and the IM and IV groups' lower means, illustrating the trend of earlier onset in the IM and IV groups compared to the Control group.

Table 12 and Figure 13: The table and accompanying bar presents the mean duration of the current episode of depression (in months) and the standard deviation (SD) for patients across three groups: Control, IM (Intramuscular), and IV (Intravenous), as well as the overall total. The Control group has a mean duration of 6.0 months with an SD of 1.9. The IM group has a mean duration of 7.3 months with an SD of 2.2, while the IV group has a mean duration of 5.8 months with an SD of 2.8. Overall, the total mean duration of the current episode of depression across all groups is 6.3 months with an SD of 2.4. This data indicates that the IM group has the longest mean duration of the current episode, while the IV group has the shortest mean duration, with the Control group falling in between. The standard deviation varies slightly across the groups, showing some differences in the variability of episode duration among the patients. The accompanying bar chart further illustrates these findings,

with the Control group showing a mean duration of 6.0 months, the IM group indicating the longest mean duration of 7.3 months, and the IV group displaying the shortest mean duration of 5.8 months. The overall mean duration of the current episode across all groups is represented at 6.3 months, highlighting the IM group's longer duration compared to the other groups.

Table 13 and Figure 14: The table and accompanying bar chart present a comparison of MADRS scores between baseline and four hours post-ketamine (T-4 hrs) across four intramuscular sessions in the IM group. In Session 1, the mean baseline MADRS score is 37.80 (SD = 6.11), which decreases to 34.17 (SD = 6.03) at T-4 hours, with a t-value of 3.28 and a p-value of 0.041, indicating a significant reduction in depressive symptoms. Session 2 shows a mean baseline score of 34.17 (SD = 5.76), decreasing to 31.07 (SD = 5.63) at T-4 hours, with a t-value of 3.49 and a p-value of 0.046, also demonstrating a significant reduction. In Session 3, the mean baseline score of 31.07 (SD = 5.63) further decreases to 26.13 (SD = 5.14) at T-4 hours, with a t-value of 5.00 and a p-value of 0.023, reflecting significant improvement. Finally, in Session 4, the mean baseline score is 26.13 (SD = 5.14), dropping to 20.02 (SD = 4.54) at T-4 hours, with a t-value of 6.84 and a p-value of 0.009, indicating the most significant reduction among the sessions. Overall, the data show a consistent and statistically significant decrease in mean MADRS scores from baseline to T-4 hours post-ketamine across all sessions, suggesting a substantial reduction in depressive symptoms over multiple sessions in the intramuscular group. The bar chart visually reinforces these findings, with blue bars representing the baseline mean MADRS scores and red bars representing the mean MADRS scores at T-4 hours. Session 1 shows a decrease from a mean baseline score of 37.80 to 34.17 at T-4 hours. Session 2 shows a reduction from a mean baseline score of 34.17 to 31.07 at T-4 hours. Session 3 shows a further reduction from a mean baseline score of 31.07 to 26.13 at T-4 hours. Finally, Session 4 shows

the most significant decrease, from a mean baseline score of 26.13 to 20.02 at T-4 hours. This consistent decrease in mean MADRS scores from baseline to T-4 hours across all sessions visually illustrates the significant reduction in depressive symptoms following ketamine administration in the intramuscular group.

Table 14 and Figure 15: Summarizes the results of paired t-tests conducted across four sessions, assessing the mean differences between baseline and post-ketamine measurements on the MADRS. In Session 1, the mean difference between baseline and post-ketamine measurements was 3.63 units, with a standard deviation (SD) of 1.04, and a t-value of 20.11, indicating a highly significant difference ($p < 0.001$). Session 2 showed a mean difference of 6.73 units (SD = 1.35) with a t-value of 28.88 ($p < 0.001$), further demonstrating a significant reduction. In Session 3, the mean difference increased to 11.67 units (SD = 2.43), with a t-value of 27.72 ($p < 0.001$), reflecting a substantial improvement. Finally, in Session 4, the mean difference was 17.78 units (SD = 2.71), with a t-value of 37.90 ($p < 0.001$), indicating the most significant reduction among the sessions. Overall, all sessions showed highly significant mean differences between baseline and post-ketamine measurements on the MADRS, with the magnitude of the mean difference and the t-values increasing across the sessions, indicating a consistent and substantial reduction in depressive symptoms over time. Figure illustrates the mean differences in MADRS scores between baseline and post-ketamine measurements across four sessions. Each bar represents a session, with the height indicating the magnitude of the mean difference. In Session 1, the mean difference is 3.63 units, which is the smallest reduction observed. Session 2 shows an increased mean difference of 6.73 units, indicating a greater reduction in depressive symptoms. Session 3 has an even larger mean difference of 11.67 units, reflecting a substantial improvement. Finally, Session 4 exhibits the highest mean difference of 17.78 units, demonstrating the most significant reduction in depressive symptoms.

Table 15: Table 15 presents the mean reduction and percentage reduction of the MADRS score following a series of intramuscular ketamine sessions. The mean reduction in MADRS score from baseline to T-4 hours in Session 4 is 17.78 units. This reduction translates to a substantial 47.04% decrease relative to the baseline MADRS score. These findings highlight a significant improvement in depressive symptoms, demonstrating the effectiveness of intramuscular ketamine in reducing MADRS scores substantially by the fourth session. This notable decrease underscores the potential therapeutic benefits of intramuscular ketamine for patients experiencing depression.

Table 16 and Figure 16: Presents a comparative analysis of the MADRS scores between baseline and four hours post-ketamine (T-4 hrs) across four infusion sessions in the intravenous group. In Session 1, the mean baseline MADRS score is 43.13 (SD = 4.91), which significantly decreases to 38.93 (SD = 5.01) at T-4 hours, with a t-value of 3.28 and a p-value of 0.032. Session 2 shows a mean baseline score of 37.93 (SD = 5.01), reducing to 34.07 (SD = 4.84) at T-4 hours, with a t-value of 3.04 and a p-value of 0.03, indicating a significant reduction. In Session 3, the mean baseline score of 32.07 (SD = 4.84) further decreases to 29.47 (SD = 4.01) at T-4 hours, with a t-value of 5.00 and a p-value of 0.025, reflecting significant improvement. Finally, in Session 4, the mean baseline score of 26.47 (SD = 4.01) drops to 22.13 (SD = 3.68) at T-4 hours, with a t-value of 6.84 and a p-value of 0.008, indicating the most significant reduction among the sessions. Overall, there is a consistent and statistically significant decrease in the mean MADRS scores from baseline to T-4 hours post-ketamine across all sessions, suggesting a substantial reduction in depressive symptoms over time with intravenous ketamine administration.The accompanying bar chart visually represents the mean MADRS scores at baseline and four hours post-ketamine (T-4 hrs) across the four infusion sessions in the intravenous group. The blue bars denote the baseline mean MADRS scores, while the red bars denote the mean

MADRS scores at T-4 hours. In Session 1, the mean baseline MADRS score decreases from 43.13 to 38.93 at T-4 hours. In Session 2, the reduction is from 37.93 to 34.07 at T-4 hours. Session 3 shows a decrease from 32.07 to 29.47 at T-4 hours, and Session 4 exhibits the most significant reduction, with the mean baseline score decreasing from 26.47 to 22.13 at T-4 hours. This consistent decrease in mean MADRS scores from baseline to T-4 hours across all sessions demonstrates a substantial and statistically significant reduction in depressive symptoms following intravenous ketamine administration.

Table 17 and Figure 17: Summarizes the results of a paired t-test analysis conducted across four sessions, comparing the mean differences between baseline and post-ketamine measurements on the MADRS. In Session 1, the mean difference between baseline and post-ketamine measurements is 4.2 units, with a standard deviation (SD) of 1.17, a t-value of 19.59, and a p-value of less than 0.001. Session 2 shows a mean difference of 9.06 units (SD = 1.43), with a t-value of 34.57 and a p-value of less than 0.001. In Session 3, the mean difference is 13.66 units (SD = 3.02), with a t-value of 24.79 and a p-value of less than 0.001. Session 4 exhibits the highest mean difference of 21.00 units (SD = 3.78), with a t-value of 30.31 and a p-value of less than 0.001. These results indicate a significant reduction in MADRS scores from baseline to post-infusion in each session, with all p-values indicating statistical significance ($p < 0.05$). Figure illustrates the mean differences in MADRS scores between baseline and post-ketamine measurements across four sessions. Each session shows a significant reduction in MADRS scores, represented by the increasing heights of the bars. In Session 1, the mean difference is 4.2 units, which increases to 9.06 units in Session 2. Session 3 shows a further increase to 13.66 units, and Session 4 exhibits the highest mean difference of 21.00 units. This consistent and substantial decrease across all four sessions highlights the effectiveness of ketamine in reducing depressive symptoms over time.

Table 18: Illustrates the mean reduction and percentage reduction of MADRS scores following a series of intravenous ketamine sessions. The mean reduction indicates an average decrease in MADRS scores from baseline to T-4 hours in Session 4, amounting to 21 units. This mean reduction translates to a 48.69% decrease relative to the baseline MADRS score. These findings underscore a substantial decrease in depressive symptoms as measured by the MADRS score after the fourth session of intravenous ketamine, highlighting its significant therapeutic effect. This notable reduction in MADRS scores demonstrates the efficacy of intravenous ketamine in significantly alleviating depressive symptoms, thereby offering a promising treatment option for patients suffering from depression.

Table 19 and Figure 18: Presents the results of independent samples t-tests comparing the mean differences in MADRS scores between the Intramuscular (IM) and Intravenous (IV) groups across four sessions. In Session 1, the IM group had a mean difference of 3.63 (SD = 1.04), while the IV group had a mean difference of 4.2 (SD = 1.17), with a t-value of -1.26 and a p-value of 0.11, indicating no significant difference. Session 2 showed a mean difference of 6.73 (SD = 1.35) for the IM group and 9.06 (SD = 1.43) for the IV group, with a t-value of -4.11 and a p-value of 0.08, approaching statistical significance and suggesting a larger mean difference in the IV group. In Session 3, the IM group had a mean difference of 11.67 (SD = 2.43), while the IV group had a mean difference of 13.66 (SD = 3.02), with a t-value of -1.78 and a p-value of 0.10, indicating no significant difference. Session 4 recorded a mean difference of 17.78 (SD = 2.71) for the IM group and 21 (SD = 3.78) for the IV group, with a t-value of -2.08 and a p-value of 0.06, also not reaching statistical significance. Overall, only Session 2 approached statistical significance, highlighting a larger mean difference in the IV group compared to the IM group, while the other sessions did not show statistically significant differences. The accompanying bar chart (Figure 19) visually illustrates

the comparison of mean differences in MADRS scores between the IM and IV groups across four sessions. In Session 1, the IM group has a mean difference of 3.63, while the IV group has a slightly higher mean difference of 4.2, with no significant difference between the groups. Session 2 shows a notable increase in the mean difference for both groups, with the IM group at 6.73 and the IV group significantly higher at 9.06, approaching statistical significance. In Session 3, the mean difference further increases to 11.67 for the IM group and 13.66 for the IV group, yet again without a significant difference. Session 4 shows the highest mean differences, with the IM group at 17.78 and the IV group at 21.0, which, although not statistically significant, indicates a substantial reduction in MADRS scores for both groups. The overall trend highlights a consistent increase in the mean differences across sessions, with the IV group showing slightly higher reductions in MADRS scores compared to the IM group.

Table 20 and Figure 19: Presents a statistical analysis of the mean values and standard deviations (SD) for three groups—Intramuscular (IM), Intravenous (IV), and Control—across five intervals: Baseline and four subsequent sessions. At baseline, the mean values were 37.80 (SD = 6.11) for the IM group, 43.13 (SD = 4.91) for the IV group, and 30.77 (SD = 3.83) for the Control group, with a highly significant F-statistic of 45.09 (p = 0.001). In the first session, the mean values decreased to 34.17 (SD = 6.03) for IM, 38.93 (SD = 5.01) for IV, and remained at 30.77 (SD = 3.83) for the Control group, showing significant differences with an F-statistic of 19.89 (p = 0.003). During the second session, the mean values were 31.07 (SD = 5.63) for IM, 34.07 (SD = 4.84) for IV, and 30.07 (SD = 3.76) for Control, again showing significant differences (F-statistic = 5.63, p = 0.04). In the third session, the mean values were 26.13 (SD = 5.14) for IM, 29.47 (SD = 4.01) for IV, and 30.73 (SD = 3.83) for Control, with an F-statistic of 9.96 (p = 0.031). By the fourth session, the mean values further decreased to 20.02 (SD = 4.54) for IM, 22.13 (SD = 3.68) for IV, while the

Control group's mean remained relatively high at 31.53 (SD = 3.94), resulting in a significant F-statistic of 68.9 (p = 0.002). The one-way ANOVA results consistently demonstrate statistically significant differences among the IM, IV, and Control groups across all intervals, confirming that the variations in group means are unlikely due to random chance. The figure illustrates the mean values and standard deviations (SD) of three groups—Intramuscular (IM), Intravenous (IV), and Control—across five intervals: Baseline and four subsequent sessions. At baseline, the IM group starts at a mean of 37.80 (SD = 6.11), the IV group at 43.13 (SD = 4.91), and the Control group at 30.77 (SD = 3.83). In the first session, there is a reduction in mean values to 34.17 (SD = 6.03) for IM and 38.93 (SD = 5.01) for IV, while the Control group's mean remains at 30.77 (SD = 3.83). This trend continues in the second session with IM at 31.07 (SD = 5.63), IV at 34.07 (SD = 4.84), and Control at 30.07 (SD = 3.76). By the third session, the mean values further decline to 26.13 (SD = 5.14) for IM, 29.47 (SD = 4.01) for IV, and slightly increase for Control to 30.73 (SD = 3.83). In the fourth session, the IM group's mean drops to 20.02 (SD = 4.54), the IV group to 22.13 (SD = 3.68), while the Control group's mean remains higher at 31.53 (SD = 3.94).

Table 21 and Figure 20: Presents the results of a paired t-test analysis comparing baseline and 60-minute post-ketamine measurements on the Clinician-Administered Dissociative States Scale (CADSS) across four sessions. Each session's data include the means and standard deviations (SD) for baseline and 60 minutes post-ketamine. In Session 1, the mean CADSS score increased from 0.20 (SD = 0.41) at baseline to 4.27 (SD = 1.78) at 60 minutes, with a t-value of 17.26 and a p-value of 0.001. Session 2 showed a rise in the mean score from 0.17 (SD = 0.38) to 4.80 (SD = 1.52), yielding a t-value of 22.89 and a p-value of 0.001. Session 3 saw an increase from 0.23 (SD = 0.43) to 4.53 (SD = 2.27), with a t-value of 14.42 and a p-value of 0.001. Finally, in Session 4, the mean score went from 0.17 (SD = 0.38) to 4.63 (SD = 1.81), resulting in a t-value of

18.68 and a p-value of 0.001. These findings indicate substantial and statistically significant increases in CADSS scores from baseline to 60 minutes post-ketamine across all four sessions, as evidenced by the high t-values and extremely low p-values (all < 0.05). The accompanying figure visually illustrates the mean CADSS scores at baseline and 60 minutes post-ketamine across four sessions. Each session shows a significant increase in the mean scores from baseline (blue bars) to 60 minutes post-ketamine (red bars). Specifically, Session 1 shows a rise from 0.20 to 4.27, Session 2 from 0.17 to 4.80, Session 3 from 0.23 to 4.53, and Session 4 from 0.17 to 4.63. This consistent pattern of elevated CADSS scores post-ketamine indicates substantial and statistically significant increases in dissociative symptoms across all sessions. The figure visually confirms these findings, showcasing the marked differences between baseline and post-treatment scores in all four sessions.

Table 22 and Figure 21: Presents the results of paired t-tests comparing baseline and post-ketamine CADSS scores across four sessions, indicating substantial and statistically significant increases in CADSS scores after ketamine administration. In Session 1, there was a mean difference of 4.07 units with a standard deviation (SD) of 1.23, resulting in a t-value of 18.12 and a p-value of less than 0.001, signifying a highly significant difference. Session 2 showed an even higher mean difference of 4.60 units (SD = 1.32), with a t-value of 19.10 and a p-value of less than 0.001, confirming a highly significant increase. Session 3 had a mean difference of 4.33 units (SD = 1.30), yielding a t-value of 18.23 and a p-value of less than 0.001, once again indicating a significant difference. Lastly, Session 4 demonstrated a mean difference of 4.43 units (SD = 1.74), with a t-value of 13.94 and a p-value of less than 0.001, showing a highly significant increase. The consistent and substantial increases in CADSS scores across all sessions underscore the significant dissociative effects of ketamine. Figure visually illustrates these findings, showing the mean differences in CADSS scores from baseline to post-ketamine across

the four sessions. Session 1 shows the smallest mean difference at 4.07 units, while Session 2 exhibits the highest mean difference at 4.60 units. Session 3 follows closely with a mean difference of 4.33 units, and Session 4 demonstrates a mean difference of 4.43 units. All sessions exhibit significant increases in CADSS scores post-ketamine, indicating the consistent and substantial effect of ketamine across multiple sessions.

Table 23 and Figure 22: Presents the results of paired t-tests comparing baseline and 60-minute post-ketamine CADSS scores across four sessions. In Session 1, the mean CADSS score increased significantly from a baseline of 0.13 (SD = 0.35) to 7.53 (SD = 2.58) post-ketamine, yielding a t-value of 15.55 ($p < 0.01$). Similarly, Session 2 showed a significant rise from 0.07 (SD = 0.25) to 7.43 (SD = 2.24), with a t-value of 44.89 ($p < 0.01$). In Session 3, the mean CADSS score increased from 0.20 (SD = 0.41) to 6.90 (SD = 1.88), resulting in a t-value of 19.09 ($p < 0.01$). Session 4 also demonstrated a significant increase from a baseline of 0.13 (SD = 0.35) to 6.43 (SD = 1.79), with a t-value of 18.91 ($p < 0.01$). These results indicate highly significant differences between baseline and post-ketamine CADSS scores across all four sessions, underscoring the substantial impact of ketamine on CADSS scores. The accompanying figure visually illustrates these significant differences, showing a marked increase in CADSS scores 60 minutes post-ketamine administration compared to baseline across all sessions. In Session 1, the mean score increases from 0.13 to 7.53, in Session 2 from 0.07 to 7.43, in Session 3 from 0.20 to 6.90, and in Session 4 from 0.13 to 6.43. These substantial increases are statistically significant, as evidenced by the high t-values and p-values less than 0.01 for all sessions, highlighting the consistent and pronounced impact of ketamine on CADSS scores.

Table 24 and Figure 23: Presents the paired t-test results comparing baseline and post-ketamine CADSS measurements across four sessions. In Session 1, the mean difference was 7.40 units (SD = 2.14), with a t-value of 18.95 ($p < 0.001$), indicating a highly significant increase in

CADSS scores post-ketamine. Session 2 showed a similar pattern, with a mean difference of 7.30 units (SD = 2.20) and a t-value of 18.20 ($p < 0.001$), again demonstrating a significant increase. In Session 3, the mean difference was 6.77 units (SD = 1.92), yielding a t-value of 19.37 ($p < 0.001$), further supporting the significant impact of ketamine. Finally, Session 4 had a mean difference of 6.30 units (SD = 1.72), with a t-value of 20.13 ($p < 0.001$), confirming the consistent and highly significant increase in CADSS scores across all sessions. These findings highlight the substantial and statistically significant effects of ketamine administration on CADSS scores, indicating a pronounced alteration from baseline across all four sessions. The figure visually represents the mean differences in CADSS scores from baseline to post-ketamine across four sessions. Each bar corresponds to one of the four sessions, illustrating the significant increases in scores. In Session 1, the mean difference is 7.40 units, reflecting a substantial rise in CADSS scores. Session 2 shows a mean difference of 7.30 units and the trend continues in Session 3, where the mean difference is 6.77 units. Finally, Session 4 has a mean difference of 6.30 units.

Table 25 and Figure 24: Presents the results of independent samples t-tests comparing mean differences in CADSS scores between the Intramuscular (IM) and Intravenous (IV) groups across four sessions. In Session 1, the IM group had a mean difference of 4.07 units (SD = 1.23), while the IV group had a significantly higher mean difference of 7.40 units (SD = 2.14), with a t-value of -7.37 and a p-value of 0.001. Session 2 followed a similar pattern, with the IM group's mean difference at 4.60 units (SD = 1.32) and the IV group's mean difference at 7.30 units (SD = 2.20), yielding a t-value of -5.77 and a p-value of 0.001. In Session 3, the IM group showed a mean difference of 4.33 units (SD = 1.30) compared to 6.77 units (SD = 1.92) for the IV group, with a t-value of -5.83 and a p-value of 0.004. Finally, Session 4 had mean differences of 4.43 units (SD = 1.74) for the IM group and 6.30 units (SD = 1.72) for the IV group, with a

t-value of -4.18 and a p-value of 0.007. These results consistently indicate that the IV group experienced larger mean differences in CADSS scores compared to the IM group across all sessions, underscoring statistically significant differences between the groups. The accompanying figure illustrates these differences, showing that the IV group consistently had larger mean differences in CADSS scores compared to the IM group across all four sessions. In Session 1, the IM group's mean difference was 4.07 units, while the IV group's was 7.40 units. Session 2 continued this trend with the IM group at 4.60 units and the IV group at 7.30 units. Session 3 showed the IM group at 4.33 units and the IV group at 6.77 units. Finally, Session 4 had the IM group's mean difference at 4.43 units compared to the IV group's 6.30 units. The significant t-values and p-values across all sessions highlight the consistent and statistically significant differences between the two groups, indicating that the IV group experienced more pronounced changes in CADSS scores compared to the IM group.

Table 26 and Figure 25: Presents the mean and standard deviation (SD) of a Modified Aldrete score across four sessions. In Sessions 1 and 2, the mean value is consistently 9.97 with a standard deviation of 0.18. However, in Session 3, there is a slight decrease in the mean value to 9.77, with an accompanying increase in variability, as indicated by a higher SD of 0.43. This downward trend continues in Session 4, where the mean value further decreases to 9.73, and the SD increases slightly to 0.45. Overall, the data demonstrate a gradual decline in the mean values from Session 1 to Session 4, coupled with increasing variability in the measurements. Figure visually represents these findings, illustrating the consistent high mean value of 9.97 with low variability in Sessions 1 and 2. In Session 3, the mean value drops to 9.77 with increased variability, and this trend continues in Session 4 with a further decline in the mean to 9.73 and a slight increase in variability. The figure highlights the

progressive reduction in mean values over time, along with the growing range of variability from Session 1 to Session 4.

Table 27 and Figure 26: Presents the mean values and standard deviations (SD) of a Modified Aldrete score measured across four infusion sessions. In Session 1, the mean value is 9.77 with a standard deviation of 0.43. This value shows a slight decrease in Session 2 to 9.70 (SD = 0.47) and continues to decline in Session 3 to 9.63 (SD = 0.49). However, there is an increase in the mean value in Session 4, reaching 9.80 with a standard deviation of 0.41. Throughout the sessions, the standard deviations remain relatively consistent, indicating stable precision in the measurements across all four sessions. This pattern suggests a slight fluctuation in the mean values over time, with the highest variability observed in Session 3. Figure illustrates the mean values of a specific variable across four infusion sessions, corresponding to the data presented in Table 27. Initially, the mean value in Session 1 is 9.77, which slightly decreases to 9.70 in Session 2. This downward trend continues in Session 3, where the mean value further decreases to 9.63. However, in Session 4, there is an increase in the mean value, rising to 9.80. The bars representing the standard deviations show that the variability in measurements remains relatively consistent across all sessions, with Session 3 having the highest standard deviation of 0.49 and Session 4 having the lowest at 0.41. Overall, the figure visually depicts the slight fluctuations in the mean values over the sessions, reflecting the stable precision in the measurements.

Table 28 and Figure 27: Present the results of t-tests comparing the Modified Aldrete scores between the intramuscular (IM) and intravenous (IV) groups across four sessions. In Session 1, the IM group had a mean score of 9.97 (SD = 0.18), while the IV group had a mean score of 9.77 (SD = 0.43), with a t-value of 2.35 and a p-value of 0.024, indicating a statistically significant difference. Similarly, in Session 2, the IM group's mean score was again 9.97 (SD = 0.18), whereas the IV group's mean

score was 9.70 (SD = 0.47), showing a significant difference (t = 2.93, p = 0.006). In Session 3, the mean scores were 9.77 (SD = 0.43) for the IM group and 9.63 (SD = 0.49) for the IV group, with no significant difference (t = 1.18, p = 0.243). Finally, in Session 4, the mean scores were 9.73 (SD = 0.45) for the IM group and 9.80 (SD = 0.41) for the IV group, also showing no significant difference (t = -0.63, p = 0.532). The significant differences in Sessions 1 and 2 indicate variability in Modified Aldrete scores between the groups during these sessions, while the lack of significant differences in Sessions 3 and 4 suggests similar recovery profiles for both groups in these later sessions. The figure visually illustrates the Modified Aldrete scores between the IM and IV groups across four sessions. In Session 1, the IM group achieved a higher mean score of 9.97 compared to 9.77 in the IV group. Similarly, in Session 2, the IM group's mean score was 9.97, while the IV group's score was 9.70. However, in Session 3, the scores were closer, with the IM group at 9.77 and the IV group at 9.63. By Session 4, the scores were almost identical, with the IM group at 9.73 and the IV group at 9.80. This figure visually confirms that while the IM group had higher scores in the initial sessions, the differences between the two groups diminished over time, indicating similar recovery profiles by the final session.

Table 29 and Figure 28: Presents the results of a Spearman's rank correlation analysis examining the relationship between age and the decrease in MADRS scores. The correlation coefficient (ρ = -0.16) suggests a weak negative correlation, indicating that as age increases, MADRS scores slightly decrease. However, this relationship is not strong. The p-value of 0.22 signifies that this correlation is not statistically significant at the α = 0.05 level. Consequently, there is no strong evidence of an association between age and the decrease in MADRS scores post-ketamine injection. Figure 29 illustrates a scatter plot with a fitted line depicting the relationship between age and the decrease in MADRS scores four hours post-ketamine injection. The scatter plot shows a weak

negative linear relationship, as indicated by the slightly downward-sloping fit line. The R^2 value of 0.025 further confirms that the correlation between age and the decrease in MADRS scores is minimal. This suggests that age has a negligible effect on the reduction of MADRS scores post-ketamine, with the data points scattered widely around the trend line, indicating considerable variability in responses regardless of age.

Table 30 and Figure 29: Presents a comparison of the mean decrease in MADRS scores post-ketamine between female and male groups, assessed using an independent t-test. The mean decrease for females is 20.19 with a standard deviation (SD) of 3.98, while for males, the mean decrease is 20.61 with an SD of 4.86. The t-value is -0.36 and the p-value is 0.78, indicating that there is no statistically significant difference in the mean decrease in MADRS scores between females and males post-ketamine injection. This suggests that gender does not significantly affect the reduction in MADRS scores following ketamine treatment. The figure illustrates the mean decrease in MADRS scores post-ketamine for female and male groups, along with their respective standard deviations. Females exhibited a mean decrease of 20.19 with an SD of 3.98, while males showed a slightly higher mean decrease of 20.61 with an SD of 4.86. Despite the visual difference in the bar heights, the independent t-test results (t-value = -0.36, p-value = 0.78) indicate no statistically significant difference between the two groups.

Table 31 and Figure 30: Presents the results of an independent samples t-test comparing mean MADRS score reductions post-ketamine between individuals with no family history of depression and those with a family history. The mean reduction for individuals with no family history is 19.95 with a standard deviation (SD) of 3.99, while for those with a family history, the mean reduction is slightly higher at 20.56 with an SD of 4.49. The t-value is -0.56, and the p-value is 0.60, indicating that the difference in mean reductions between the two groups is not statistically significant. This suggests that having a family history of depression does not

significantly impact the decrease in MADRS scores following ketamine treatment. Figure illustrates the mean decrease in MADRS scores of patients with and without a family history of psychiatric illness following ketamine treatment. The figure clearly shows that the mean decrease in MADRS scores is higher for patients with a positive family history compared to those with no family history. This indicates that patients with a family history of psychiatric illness experienced a greater reduction in depressive symptoms post-ketamine treatment. However, it's important to note that despite this observed difference, the statistical analysis, as presented in the corresponding table, indicated that this difference was not significant (p-value = 0.60). Therefore, while the figure visually highlights a greater mean reduction for those with a family history, the evidence does not support a strong association between family history and the extent of decrease in MADRS scores.

Table 32 and Figure 31: Presents the descriptive statistics and results of an ANOVA analysis for post-ketamine CADSS scores categorized by occupation. The mean scores and standard deviations (SD) for each occupational group are as follows: Professionals had a mean score of 4.62 (SD = 2.33), Semi-Skilled workers had a mean score of 4.45 (SD = 1.85), Semi-Professionals had a mean score of 3.14 (SD = 1.07), Skilled workers had a mean score of 5.54 (SD = 2.38), and the Unemployed group had the highest mean score of 5.68 (SD = 1.36). The ANOVA yielded an F-value of 8.94 with a p-value of 0.11, indicating that there is no statistically significant difference in post-ketamine CADSS scores among the different occupational groups at the 0.05 significance level. Figure illustrates the mean post-ketamine CADSS scores for various occupational groups, represented by blue bars. This figure highlights the differences in post-ketamine dissociative symptoms among professionals, semi-skilled workers, semi-professionals, skilled workers, and unemployed individuals. The data shows that unemployed individuals and those in skilled occupations exhibit higher mean CADSS scores, suggesting they

experience greater dissociative symptoms post-ketamine. In contrast, semi-professionals have the lowest mean scores, indicating fewer dissociative symptoms compared to the other groups. This visual representation underscores the variation in post-ketamine effects across different occupational categories.

Table 33: Presents a comparative analysis of patients with a family history of psychiatric illnesses who received intravenous ketamine versus those in the control group. The independent t-test results indicate no statistically significant differences in several metrics. The mean duration of the current depressive episode was 6.6 ±2.7 months for the intravenous ketamine group and 6.1 ±2.0 months for the control group ($t = 0.098$, $p = 2.8$). The mean age of onset of depression was 33.67 ±4.99 years for the intravenous ketamine group and 36.70 ±5.51 years for the control group ($t = 0.51$, $p = 0.42$). Additionally, the mean number of lifetime episodes was 1.97 ±0.69 for the intravenous ketamine group and 1.87 ±0.68 for the control group ($t = 0.33$, $p = 0.56$). These results suggest that there are no significant differences between the two groups in terms of the duration of the current depressive episode, age of onset of depression, and the number of lifetime depressive episodes.

Table 34 and Figure 32: Presents the results of a Spearman's rank correlation analysis examining the relationship between the decrease in MADRS scores after intravenous ketamine treatment and the age of onset of depression. The Spearman's rank correlation coefficient was 0.209, indicating a weak positive correlation. However, the p-value of 0.267 suggests that this relationship is not statistically significant, meaning there is no strong evidence to support an association between the decrease in MADRS scores post-ketamine and the age at which depression first occurred. Figure illustrates a scatter plot depicting the relationship between the decrease in MADRS scores after intravenous ketamine treatment and the age of onset of depression. The plot reveals no meaningful linear relationship between these two variables, as evidenced

by the near-horizontal trend line. The distribution of data points indicates a lack of correlation, supported by the negligible R-squared value of 3.672E-5, further emphasizing that changes in MADRS scores are not associated with the age at which depression first occurred.

Table 35 and Figure 33: Presents the results of a Spearman's rank correlation analysis examining the relationship between the decrease in MADRS scores after intravenous ketamine treatment and the duration of the current episode of depression. The Spearman's rank correlation coefficient was calculated to be -0.192, indicating a weak negative correlation. This suggests that as the duration of the current episode of depression increases, the decrease in MADRS scores post-ketamine slightly diminishes. However, the p-value of 0.311 indicates that this relationship is not statistically significant, implying that there is no strong evidence to support an association between these two variables. Figure 35 depicts a scatter plot showing the relationship between the decrease in MADRS scores after intravenous ketamine treatment and the duration of the current episode of depression (measured in months). The trend line, which is almost horizontal, suggests that there is no significant linear relationship between these two variables. This observation is further supported by the Spearman's rank correlation coefficient of -0.192 and a p-value of 0.311, as indicated in Table 35. The points on the scatter plot are widely dispersed without any clear pattern, reinforcing the conclusion that the duration of the current episode of depression does not significantly correlate with the decrease in MADRS scores following ketamine treatment.

Table 36: The provided table displays the results of a statistical analysis examining the relationship between the decrease in MADRS scores after intravenous ketamine treatment and the number of lifetime episodes of depression. The analysis employs Spearman's rank correlation coefficient to assess this relationship. The Spearman's rank correlation coefficient of 0.421 indicates a moderate positive correlation between the decrease in

MADRS scores following ketamine treatment and the number of lifetime episodes, suggesting that as the number of lifetime episodes increases, there is a tendency for a greater reduction in MADRS scores post-treatment. However, the p-value of 0.21 indicates that the correlation is not statistically significant implying that there is insufficient evidence to conclude the observed correlation. Overall, while there is a moderate positive correlation between the variables, the lack of statistical significance suggests that the relationship should be interpreted with caution.

Table 37 : Presents a comparative analysis of patients with a family history of psychiatric illnesses who received intramuscular ketamine versus those in the control group. The mean duration of the current episode was 7.23 ±2.17 months for the intramuscular group and 6.10 ± 2.00 months for the control group, with a t-value of 0.28 and a p-value of 1.14, indicating no significant difference. The mean age of onset of depression was 33.93 ±5.55 years for the intramuscular group and 36.70 ±5.51 years for the control group, with a t-value of 0.71 and a p-value of 0.13, also indicating no significant difference. Additionally, the mean number of lifetime episodes was 2.13 ±0.62 for the intramuscular group and 1.87 ±0.68 for the control group, with a t-value of 0.59 and a p-value of 0.27, showing no significant difference between the groups. These results suggest that there are no significant differences between the two groups in terms of the duration of the current depressive episode, age of onset of depression, and the number of lifetime depressive episodes.

Table 38 and Figure 34: Presents the results of a Spearman's rank correlation analysis between the decrease in MADRS scores following intramuscular ketamine treatment and the age of onset of depression. The analysis reveals a Spearman's rank correlation coefficient of -0.198, indicating a weak negative correlation. This suggests that as the age of onset of depression increases, the reduction in MADRS scores slightly decreases. However, this relationship is not statistically significant, as

evidenced by a p-value of 0.294, implying that there is no strong evidence to support a meaningful association between these variables. Figure illustrates a scatter plot depicting the relationship between the decrease in MADRS scores and the age of onset of depression. The trend line in the scatter plot shows a slight downward slope, suggesting a weak negative linear relationship. However, the wide dispersion of data points around the trend line indicates significant variability and a lack of a strong correlation. This visual representation aligns with the statistical findings, reinforcing the conclusion that the age of onset of depression does not significantly influence the reduction in MADRS scores following intramuscular ketamine treatment.

Table 39 and Figure 35: Presents the Spearman's rank correlation analysis between the decrease in MADRS scores after intramuscular ketamine treatment and the duration of the current episode of depression. The Spearman's rank correlation coefficient was calculated to be -0.291, indicating a weak negative correlation between the two variables. This suggests that as the duration of the current episode of depression increases, the decrease in MADRS scores post-ketamine treatment slightly decreases. However, the p-value of 0.118 indicates that this relationship is not statistically significant, meaning there is no strong evidence to support an association between the duration of the current episode of depression and the decrease in MADRS scores following intramuscular ketamine treatment. Figure illustrates a scatter plot depicting the relationship between the decrease in MADRS scores after intramuscular ketamine treatment and the duration of the current episode of depression. The plot shows a weak negative linear relationship, as indicated by the downward trend of the fit line. This suggests that as the duration of the current depressive episode increases, the reduction in MADRS scores following ketamine treatment slightly decreases. However, the spread of data points and the weak slope of the trend line imply that this relationship is not strong.

Table 40 and Figure 36: Presents the results of the Spearman's rank correlation analysis between the decrease in MADRS scores after intramuscular ketamine treatment and the number of lifetime episodes of depression. The Spearman's rank correlation coefficient was calculated to be 0.140, indicating a very weak positive correlation between the two variables. This suggests that there is a slight, but not substantial, association between a greater number of lifetime episodes of depression and a more significant decrease in MADRS scores following intramuscular ketamine treatment. However, the p-value of 0.461 indicates that this relationship is not statistically significant, implying that there is no strong evidence to support a meaningful association between these variables. Figure 40 illustrates a scatter plot depicting the relationship between the decrease in MADRS scores after intramuscular ketamine treatment and the number of lifetime episodes of depression. The plot, accompanied by a fitted line, indicates a non-linear relationship, as evidenced by the fluctuations in the data points rather than a clear linear trend. This observation aligns with the weak correlation coefficient and the non-significant p-value, suggesting that the number of lifetime episodes does not strongly predict the decrease in MADRS scores post-treatment. This table and figure indicate that while there is some relationship between the number of lifetime episodes and the decrease in MADRS scores, it is weak and not statistically significant, suggesting that other factors may play a more substantial role in influencing the treatment outcome.

DISCUSSION

For the past two decades, ketamine combined with narcotics has been effectively used in intensive care units to help patients with terminal conditions to manage anxiety, severe depression, and suicidal ideation. The rapid antidepressant effects of ketamine have been consistently shown in various studies, including numerous RCTs. However, these effects have primarily been studied in individuals with TRD. There is a lack of research on the use of ketamine in standard healthcare settings, where patients are often receiving concurrent antidepressant medications and other treatment modalities.[76,120,115,104] Data on concurrent use of anti-depressants with ketamine has been especially even more sparse.[115,100,109] According to current information, there has been only one published RCT by **Y.D. Hu and colleagues** that investigated the efficacy of ketamine as an augmentation agent to oral antidepressant medication.[107]

Several case reports and small RCTs have indicated that IV ketamine infusions provide significant and rapid antidepressant effects. However, these benefits tend to be short-lived.[80] Research has mainly concentrated on administering ketamine intravenously. The potential use of IM ketamine for treating depression is still underexplored. In the first case report on IM ketamine, a patient with metastatic ovarian cancer received six treatments of 1 mg/kg, which resulted in reduced depressive symptoms. Another report indicated that 0.5 mg/kg of IM ketamine significantly reduced severe depressive symptoms and suicidal thoughts in two patients within a few hours. Oral ketamine has yet to be systematically studied; only two case reports suggest that a single oral dose provided quick and moderately lasting relief from depression and anxiety without adverse effects. Although IV ketamine requires a 40-minute infusion that is cumbersome, relatively expensive, and needs close monitoring, the IM route might address these issues[129]. Therefore, the present study was conducted to

analyze the effect of ketamine on patients with moderate to severe depressive disorder.

The present randomised, double blinded study included 90 subjects of MDD, who were already taking escitalopram 10-20 mg for atleast 4 weeks. They were divided into three groups; Group A received IV ketamine, Group B received IM ketamine and Group C were controls.

Majority of subjects in control group were males (n=17, 56.7%) and rest were females (n=13, 43.3%). In IM group, majority of females was noted (f/m: 18/12: 60.0%/40.0%) and same were the findings in IV group also (f/m: 21/9: 70.0%/30.0%). The mean age of subjects in control group was 44.9±9.92 years, with maximum subjects in age group 35-44 years (n=10, 33.3%). The mean age in IM group was 45.17±8.60 years, with maximum subjects aged between 45-54 years (n=13, 43.3%) and the mean age in IV group was 43.13±8.16, majority of subjects were aged between 35-44 years (n=10, 33.3%). This was comparable and consistent with the mean age of the patients participating in the study done by **Hu et al,** and the mean age in their study was 39 ±12.6 years.[107]

National Mental Health Survey (NHMS)[141] also reported higher lifetime prevalence of MDD in the age group of 40-49 years and more in females which is concordance with the present study.

According to studies done by **Tung-Ping Su et al.[114], Sachin ahuja et al** [129] and **Suprio Mandal et al.**[121], patients were predominantly females between 40 and 50 years of age, which is similar to the present study.

Harihar Chilukuri et al [80] in their study, found that the average age of the subjects was 36.81 years (SD 11.815, range 19-64). The male to female ratio was 2:7, indicating a higher prevalence of female participants.

Majority of the study subjects were married and studied up to higher secondary level in all the groups. Maximum of the study subjects in all groups were unemployed i.e., 12 (40.0%) in control group and 11 (36.7%) each in IM and IV group. Maximum study subjects in all the groups lived in nuclear families, i.e., 24 (80.0%) in control group, 27 (90.0%) in IM group

and 24 (80.0%) in IV group. Maximum study patients belonged to urban area i.e., 18 (60.0%) in control group, 24 (80.0%) in IM group and 19 (63.3%) in IV group because of catchment area of the hospital.

In a study by **Suprio Mandal et al**[121], majority of the patients were unemployed (55.0%) and married (70.0%).

In a study by **Subramani Poongothai et al. (2009)**[142] and the **NMHS survey (2016)**[141], the prevalence of depression was found to be higher in urban populations than in rural populations. Furthermore, the prevalence was higher in nuclear families compared to joint families, aligning with the findings of the present study. Due to proper randomization, there were no statistically significant differences between the study groups in terms of demographic and socio-economic parameters, ensuring that these factors did not confound the study's outcomes.

The mean age of onset of depression (first episode) in control group was 36.9±5.7 years, in IM group was 33.9±5.5 years and in IV group was 33.7±4.7 years. Mean duration of current MDD episode in control group was 6.0±1.9 months, in IM group was 7.3±2.2 months and in IV group it was 5.8±2.8 months. The highest number of patients in all groups experienced 2 depressive episodes (55.6%). The next highest group had 1 depressive episode (24.4%). The fewest patients had 3 depressive episodes (20.0%). These findings are in concordance with the results of the RCT conducted by **Hu et al.**, where the average age of onset of depression was 34.4 years, and the length of the current depressive episode was 5.1 months. Most patients in the IV ketamine group of their study experienced two depressive episodes in their lifetimes[107]. Similarly Suprio Mandal et al[121] In their study, reported that the average age of illness onset was 29.90 ± 8.73 years, and the average duration of illness was 6.95 ± 4.31 months.

MADRS is the primary scale used in our study to assess symptom severity of depressive symptoms and treatment response to medication. It is a clinician administered scale with the main advantage of having excellent

internal consistency (Cronbach's alpha = 0.86) and high sensitivity for detecting changes in depressive symptoms. The high correlation between single items and the MADRS total score highlights the scale's excellent reliability. Compared to the other scales, the MADRS may be better suited for detecting or measuring treatment effects within a homogeneous sample**[Seemüller, F et al, 2023]** [139]**.** Majority of the studies conducted on the role of ketamine as an anti-depressant have used the MADRS or HDRS as a rating tool for assessment of depressive symptoms[30]

Mean baseline MADRS scores in the present study for IM group was 37.80 ± 6.11, for IV group was 43.13± 4.91 and for control group was 30.77±3.83. The MADRS scores in both the IM and IV groups showed a statistically significant difference from baseline to t-4 hours across all four KET sessions, with p-values less than 0.05. The mean difference in MADRS scores from baseline to post-ketamine injection in each session (1, 2, 3, and 4) in the IM group was 3.63±1.04, 6.73±1.35, 11.67±2.43, and 17.78±2.71, respectively. The mean reduction in MADRS scores from baseline to the last infusion session in the IM group was 17.78, with a percentage reduction of 47.04%. In the IV group, the mean difference in MADRS scores from baseline to post-ketamine injection in each session (1, 2, 3, and 4) was 4.2±1.17, 9.06±1.43, 13.66±3.02, and 21±3.78, respectively. The mean reduction in MADRS scores from baseline to the last infusion session in the IV group was 21, with a percentage reduction of 48.69%. These findings are in concordance with the Indian study done by **Suprio Mandal et al**[121] in Central Institute of Psychiatry, Ranchi which revealed significant reduction in depression and anxiety at 1 hour after the first dose of ketamine. In a study by **Paulo R. Shiroma et al**[123],it was noted that repeated ketamine sessions demonstrated greater antidepressant efficacy, which is consistent with the results of our study. When comparing the mean values at each infusion session, no significant difference was found in the decrease in mean MADRS scores between

the IM and IV groups. The findings of our study are similar to those of the study done by **Carl J. Bonnet et al.**[143], who found that IM ketamine therapy yields immediate antidepressant effects comparable to IV therapy, with 98% of patients reporting improvement. The mean depression score (PHQ-9) decreased by 55%, PTSD symptoms (PCL-5) showed a 51% reduction, and anxiety scores (GAD-7) decreased by 51%.

Our study's findings align with several previous studies on the efficacy of ketamine in treating major depressive disorder. For instance, **Harihar Chilukuri et al**.[80] reported that administering sub-anesthetic doses of ketamine either IV or IM resulted in a significant decrease in depressive symptoms in patients with major depression at 2 hours, sustained until the 4th day post-injection. These results support our finding that both the IM and IV routes are effective for ketamine administration. Similarly, **Ahuja S, et al.** [129] described that patients with MDD receiving a median of 4 (range 1–48) IM ketamine treatments experienced a median improvement of 38% in depression scores (PHQ-9) and a 50% improvement in anxiety scores (GAD-7). These improvements were maintained for over 7 months with maintenance treatments, demonstrating that IM ketamine significantly improves depression and anxiety without regression during maintenance. Our study concurs with these findings, as we observed a markedly decrease in depressive symptoms in patients treated with IM ketamine, comparable to those receiving IV ketamine. Overall, the results from our study, along with the findings from **Harihar Chilukuri et al.**[80] and **Ahuja S, et al.** [129], underscore the efficacy of both IM and IV routes for ketamine administration in significantly improving symptoms of depression in patients with MDD.

In our study, we administered ketamine to two groups of patients, using IM and IV routes, while they were also receiving escitalopram therapy. A third group served as the control group and received only escitalopram without ketamine. There have been very few studies in India comparing the effectiveness of ketamine administered through IV and IM routes. Our

findings indicated significant improvement in symptoms of depression in both ketamine groups compared to the control group. The findings of our study were in concordance with findings of The RCT conducted by **Hu et al** [107] which made concurrent use of escitalopram in patients during the trial found that that none of the patients in the control group showed response at the 24 hours 'time period as compared to more than two thirds of the patients showing response in the group receiving ketamine. More than ninety percent of the patients who had received ketamine had shown response as compared to less than twenty percent response observed in the control group at the 7 day assessment.[101] Finding of our study is comparable to findings of study done by **Hu et al** [107] which shows more response in ketamine group as compared to control group. Similarly in a RCT trial by **Zarate et al**[104]**,** a rapid reduction in HAM-D scores indicated an overall improvement in depressive symptoms, supporting the rapid antidepressant effect of ketamine.[62]. In another RCT by **Sos P et al** [106], involving 27 patients with MDD, a single intravenous dose of ketamine resulted in a significant reduction in symptom severity compared to placebo, with the peak effect observed within 24 hours.

Current research on the repeated dosing of ketamine is limited. This study investigated long-term repeated doses of ketamine and found a significant reduction in depression scores during regular follow-ups. Similar outcomes were observed in an open-label study involving patients with major depressive disorder (MDD); those who responded to a single IV ketamine dose continued to show improvement after receiving a total of six doses over 12 days, despite the study's small sample size.**[Aan Het Rot M et al][103].** A RCT involving 67 patients with TRD demonstrated a significant reduction in symptoms of depression through twice or thrice-weekly ketamine infusions over a fifteen day period **[Singh JB et al][109]** Both studies mentioned above administered ketamine via IV infusion over 40 minutes.

No association was found between age, and decrease in MADRS score after giving ketamine injection. In our study ketamine shows immediate improvement in depressive symptoms in both IV and IM group irrespective of age of patients and the overall decrease in MADRS score was similar in all age groups. However **Pennybaker S, et al.**[144] in their study found that age influences the antidepressant effects of serial ketamine infusions in TRD, with older patients experiencing significant improvement later in the treatment course compared to younger patients. Despite age-related delays, both older and younger patients ultimately experienced similar overall improvements. Hence, age may mediate the speed but not the durability or total efficacy of ketamine treatment, suggesting that dissociable mechanisms may underlie differing aspects of ketamine's antidepressant activity. Similarily no association was found between gender and the decrease in MADRS score after administering ketamine injections in our study. This is in concordance with the study done by **Zheng W et al.** [130] whose findings indicate that the rates of antianhedonic response and remission to multiple ketamine infusions for treating depression were similar between males and females.

No association was found between presence or absence of family history of psychiatric illnesses and decrease in MADRS score after giving ketamine injection in our study however study done by **Schwartz J et al 2016** **[111]** found that patients having family history of alcohol use disorder and anxious depression respond better to ketamine. Research is underway examining biological predictors of response to ketamine, including genetic, central neurobiological and peripheral measures, but it is premature to recommend their adoption in clinical practice.

Similarly, no association was found between the occupation of subjects and dissociative symptoms on the CADSS after administering ketamine in our study. An observational study done by **Włodarczyk A et al. (2021)** [124] provides no support for the association between CADSS score and treatment outcome with MADRS, nor was any direct relation found

between other demographic variables. However, the study may be underpowered due to the small sample size. Similarly in both the IV and IM groups, no relationship was found between the decrease in MADRS score and the age of onset of depression, duration of the depressive episode, or number of lifetime episodes after administering ketamine. Due to lack of literature, we were not able to compare to other variables with past studies.

Recent literature, considering ketamine's pharmacokinetics and strong safety profile, explores its mechanisms of action in alleviating depression. Glutamate, a key excitatory neurotransmitter, is essential for brain cell activation. Ketamine functions by directly blocking NMDA receptors (NMDARs), which leads to an increase in glutamate levels in the brain. Additionally, other studies have found that ketamine affects various other brain molecules, indicating that it may initiate downstream biological changes that contribute to its antidepressant effects[80].

In the past 12 years, numerous studies have suggested that a new class of drugs targeting the glutamatergic neurotransmitter system could provide rapid and robust antidepressant effects, especially for patients who have not responded to traditional monoaminergic antidepressant medications. A recent review offers a detailed overview of several ongoing clinical trials in this field**[122]** Ketamine is reported to alleviate symptoms of depression by activating the mTOR, leading to an increase in synapse-related proteins.**[27]**

In the present study, there was a significant decrease in suicidal ideation reported on the MADRS scale following ketamine sessions. Both the IM and IV groups showed a significant reduction in suicidal ideation compared to the control group. This indicates that ketamine has a rapid anti-suicidal effect in both treatment groups, with significant improvement in suicidal ideation sustained throughout the course of four sessions.**Pathak U, et al.**[145] found significant reductions in HAM-D17 and MSSI scores within 6 hours of the first dose in the ketamine group

compared to the normal saline group. The improvement was sustained for up to one week, which aligns with the results of our study. Similarly, **Price RB et al.** [101] found a significant reduction in MADRS suicide item scores observed 24 hours after a single infusion of ketamine in 23 patients with TRD. In additional group of nine patients, the effect persisted for 12 days with thrice-weekly ketamine infusions, likely due to the drug's strong antidepressant properties. Our study also showed a significant reduction in suicidal ideation after the fourth ketamine session, reinforcing these findings.

Furthermore, **Diaz Granados N et al.**[102] did a study involving 33 patients with treatment-resistant MDD who received a ketamine infusion (0.5 mg/kg) reported a significant reduction in suicidal ideation ratings, as well as in MADRS and HAM-D suicide item scores, from 40 minutes to 4 hours post-infusion. Our study's findings align with those of Pathak U et al., Price RB et al., and Diaz Granados N et al., all of which show that ketamine has a rapid and sustained anti-suicidal effect in patients with MDD, regardless of the administration route.

In accordance with previous studies, subjects in Group A and B experienced mild and transient increase in measures of dissociation during the first and all subsequent infusions. Ketamine in IM group resulted in significant increase in symptoms as measured by CADSS with Session 1 showed a mean difference of 4.07 units with $p < 0.001$, Session 2 had a mean difference of 4.60 units with $p < 0.001$. In Session 3, the mean difference was 4.33 units with $p < 0.001$. Session 4 showed a mean difference of 4.43 units with a $p < 0.001$. Similarly in IV group there were increase in dissociative symptoms as measured by CADSS. In Session 1, the mean baseline value increased from 0.13 (SD = 0.35) to 7.53 (SD = 2.58) after 60 minutes, with a $p < 0.01$. Session 2 saw an increase from 0.07 (SD = 0.25) to 7.43 (SD = 2.24), with a $p < 0.01$. In Session 3, the mean rose from 0.20 (SD = 0.41) to 6.90 (SD = 1.88), yielding a $p < 0.01$.

Session 4 had a baseline mean of 0.13 (SD = 0.35), which increased to 6.43 (SD = 1.79), with a $p < 0.01$.

These dissociative symptoms were transient and returned to baseline by 120 minutes after the ketamine. This effect is consistent with that observed in previous single-dose and repeated dose ketamine studies. In a systematic review done by **Short B et al** [69] it was found that dissociation is the most frequently reported psychotomimetic side effect of ketamine, followed by perceptual disturbances, odd or abnormal sensations, derealization, hallucinations, and feelings of being strange, weird, bizarre, or unreal, as well as depersonalization. While no long-term psychotomimetic side effects were reported, most studies only assessed these effects within a short-term window (typically within 4 hours post-ketamine dose). IV administration of ketamine was associated with a higher incidence of psychotomimetic or dissociative side effects (72%) compared to non-intravenous routes (36%). In our study patients in IV group experienced more dissociative symptoms as compared to patients in IM group which is in concordance with the findings of above study.

Ketamine-induced dissociation is believed to be associated with N-methyl-D-aspartate receptor blockade and surfeit ketamine activity. Cumulative increase in severity of dissociative effects was not observed with additional infusions. Patients in Group A and B reported mild transient increase in BP and heart rate during all ketamine infusions. Blood pressure and heart rate was measured every 5 minutes throughout the time of infusion and half hourly for 2 hours after ketamine administration. There was slight increase in blood pressure and heart rate which was transient and returned to baseline within 2 hours. Only 2 patients in IV group show increase in blood pressure over 180/110 mm of Hg requiring pharmacological management by IV labetolol. In a systematic review of the 60 studies done by **Short B et al** [69], 23 (38%) reported acute changes in the cardiovascular status of patients. The most common cardiovascular changes were increased blood pressure and increased heart rate. Most

cardiovascular effects were reported as occurring during or immediately after IV ketamine administration. In general, these effects resolved within 90 min of the administered dose which is concordance with the findings of our study.

Modified aldrete score was applied to note the hemodynamic changes and to safely discharge the patients. There was no significant change in modified aldrete score among IV as well as IM group. Overall, ketamine in both the IV and IM group were tolerated well hemodynamically and none of the subjects experienced any cardiovascular system insufficiency or arrhythmias, but these results should be interpreted cautiously.

Our study's findings were similar to the study done by **Aan het Rot M et al.**[103], where patients experienced brief hypertensive episodes and developed transient tachycardia. However, these symptoms resolved 5 minutes post-infusion. In their study all hemodynamic parameters were considered manageable by the administering anesthesiologist and did not necessitate termination of the infusions.

Regardless of its mode of action, whether administered via IM or IV, ketamine can be a highly effective tool for providing immediate relief to patients who are depressed and suicidal, pending the onset of action of newly started antidepressants or the arrangement of ECT. It can be particularly useful for treating depressed patients who are unwilling to undergo ECT or for whom ECT is relatively contraindicated, such as in cases of brain tumors or recent myocardial infarction. This represents an important breakthrough in the emergency management of severe depression. Ketamine can also be beneficial for students who are severely depressed before their exams, as ECT can interfere with memory and is thus not preferred. As demonstrated in our study, the IM route is as effective as the IV route for ketamine, allowing it to be administered on an outpatient basis for severely depressed patients. However, it is recommended that patients rest for a few hours following the injection due to possible sedation and other minor adverse effects.[103]

SUMMARY AND CONCLUSION

The present randomized, double-blinded, pre- and post-intervention assessment study included 90 subjects with MDD, who had been taking escitalopram 10-20 mg for at least 4 weeks. They were divided into three groups: Group A received IV ketamine, Group B received IM ketamine, and Group C served as controls. The aim of the study was to compare the therapeutic efficacy of ketamine administered intravenously versus intramuscularly in patients with MDD.

The findings of the study are summarized as follows:

1. The majority of subjects in the control group were males (n=17, 56.7%), with the remainder being females (n=13, 43.3%). In the IM group, the majority were females (f/m: 18/12: 60.0%/40.0%), and the same was true in the IV group (f/m: 21/9: 70.0%/30.0%).
2. The mean age of subjects in the control group was 44.9±9.92 years, with the largest number of subjects in the 35-44 years age group (n=10, 33.3%). The mean age in the IM group was 45.17±8.60 years, with the majority aged between 45-54 years (n=13, 43.3%). The mean age in the IV group was 43.13±8.16 years, with the majority aged between 35-44 years (n=10, 33.3%).
3. The majority of study subjects were married across all groups, with the control group having the highest percentage of married participants at 96.7%. Both the IM and IV groups had a slightly lower but identical percentage of married participants at 93.3%.
4. The majority of participants (46.7%) had completed Higher Secondary School, with a significant portion being graduates (33.3%). In the IM group, the largest percentage were graduates (33.3%), followed closely by those with Higher Secondary School education (30.0%), and a notable percentage had completed Middle School (20.0%). In the IV group, graduates made up the largest group (36.7%), followed by participants with Higher Secondary School education (33.3%).

Overall, there was a general trend indicating that most participants had at least completed Higher Secondary School education.

5. The majority of study subjects in all groups were unemployed: 12 (40%) in the control group and 11 (36.67%) each in the IM and IV groups.
6. The majority of study subjects across all groups were from nuclear families (83.3%). The IM group had the highest percentage of nuclear family observations (90.0%), while the control and IV groups each had 80.0% of observations from nuclear families.
7. Urban participants constituted a majority in all three groups, with the IM group having the highest proportion of urban participants at 80.0%, followed by the IV group at 63.3% and the control group at 60.0%. Overall, 67.8% of the participants were from urban areas, while 32.2% were from rural areas.
8. The majority of study subjects had experienced 2 episodes of MDD: 17 (56.67%) each in the control and IM groups and 16 (53.33%) in the IV group.
9. The overall majority (70.0%) had a positive family history, with the IV and control groups showing the highest percentage (73.3%).
10. The highest number of patients in all groups had experienced 2 depressive episodes (55.6%). The next highest group had 1 depressive episode (24.4%). The fewest patients had 3 depressive episodes (20.0%).
11. In 90 patients, the mean age of onset of depression was 34.8 years with a standard deviation of 5.4. The mean age of onset of depression was slightly lower in the IV (33.7±4.7) and IM (33.9±5.5) groups compared to the control group. The control group had the highest mean age of onset (36.9) and standard deviation (5.7).
12. Of the 90 patients observed, the mean duration of the current episode of depression was 6.4 months overall with a standard deviation of 2.4. The IM group had the longest mean duration of the current episode of

depression (7.3 months), followed by the control group (6.0 months), and the IV group (5.8 months), which had the shortest mean duration.

13. The MADRS scores in both the IM and IV groups showed a statistically significant difference from baseline to 4 hours post-administration across all four KET sessions, with p-values less than 0.05.
14. The mean difference in MADRS scores from baseline to post-ketamine injection in each session (1, 2, 3, and 4) in the IM group was 3.63±1.04, 6.73±1.35, 11.67±2.43, and 17.78±2.71, respectively. The mean reduction in MADRS scores from baseline to the last infusion session in the IM group was 17.78, with a percentage reduction of 47.04%.
15. In the IV group, the mean difference in MADRS scores from baseline to post-ketamine injection in each session (1, 2, 3, and 4) was 4.2±1.17, 9.06±1.43, 13.66±3.02, and 21±3.78, respectively. The mean reduction in MADRS scores from baseline to the last infusion session in the IV group was 21, with a percentage reduction of 48.69%.
16. No significant difference was found between the decrease in mean MADRS scores in the IM and IV groups when mean values were compared at each infusion session.
17. When the mean MADRS scores were compared at baseline, 1st session, 2nd session, 3rd session, and 4th session in the IM, IV, and control groups, a statistically significant difference was found.
18. No correlation was found between age, gender, presence or absence of family history of MDD, and the decrease in MADRS scores after administering ketamine injections.
19. No correlation was found between the occupation of subjects and post-ketamine CADSS scores.
20. CADSS in both the IM and IV groups showed a statistically significant difference from baseline to 60 minutes post-administration in all four

KET sessions (p=0.001), indicating that dissociative symptoms were present in patients after the KET session. CADSS scores were higher in the IV group compared to the IM group in all four KET sessions, with a statistically significant difference.

21. There was no significant change in the modified Aldrete score in either the IV or IM group.

Conclusion: Our study demonstrated that administering ketamine at a dose of 0.5 mg/kg, whether IM or IV, is both safe and effective. This treatment led to a rapid reduction in depressive symptoms within hours, as measured by the MADRS, highlighting ketamine's crucial role in the emergency management of severe depression until better alternatives are found. Both IV and IM administration of ketamine resulted in significant improvements in depressive symptoms, noticeable as early as 4 hours after a single dose and sustained with subsequent doses over a two-week period. There was no significant difference in the reduction of mean MADRS scores between the IM and IV groups when comparing mean values at each ketamine session. This provides strong evidence for ketamine’s rapid and sustained efficacy in treating depressive disorders and its tolerability at a sub-anesthetic dose of 0.5 mg/kg, regardless of the administration route.

LIMITATIONS

The study also investigated the antidepressant effects of ketamine in subjects concurrently using escitalopram, presenting several important considerations. The simultaneous use of escitalopram, an antidepressant taken for at least four weeks, may confound the results, making it challenging to isolate the effects of ketamine alone. Furthermore, the limited diversity of participants, primarily from urban areas and nuclear families, may not represent the broader population, restricting the applicability of the results to different demographic groups. Lastly, while the study reported dissociative symptoms, it did not extensively analyze their impact on the overall treatment experience and long-term outcomes, leaving a gap in understanding the full scope of ketamine's effects.

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S.NO.	MRD NO.	NAME INITIALS	AGE	SEX	MARITAL STATUS	OCCUPATION	EDUCATION	TYPE OF FAMILY	LOCALITY
1	1222980	B.S.	46	M	Married	Skilled	Higher school	Nuclear	Rural
2	1558135	J.S.	38	M	Married	Skilled	Higher school	Nuclear	Rural
3	60418	M.K.	56	F	Married	Unemployed	Higher school	Joint	Rural
4	567821	S.K	37	F	Married	Unemployed	Higher school	Nuclear	Rural
5	185425	T.K.	48	F	Married	Unemployed	Higher school	Joint	Urban
6	784402	D.K.	41	F	Married	Unemployed	Graduate	Nuclear	Urban
7	149117	H.S.	43	M	Married	Skilled	Primary school	Nuclear	Rural
8	1566683	K.K.	48	F	Married	Unemployed	Higher school	Joint	Urban
9	1637529	V.N.	56	M	Married	Semi- Skilled	Higher school	Nuclear	Urban
10	1572453	A.D.	41	F	Married	Semi- Skilled	Graduate	Nuclear	Urban
11	1433253	N.K.	29	F	Unmarried	Skilled	Graduate	Nuclear	Urban
12	59583	J.K.	44	F	Married	Unemployed	Graduate	Nuclear	Urban
13	57691	K.S.	32	M	Married	Skilled	Higher school	Nuclear	Rural
14	52195	K.S.	54	F	Married	Unemployed	Graduate	Nuclear	Urban
15	45518	K.K.	35	F	Married	Semi- Skilled	Graduate	Nuclear	Urban
16	1345762	A.K.	49	F	Married	Semi- Skilled	Primary school	Nuclear	Urban
17	456872	K.D.	41	F	Married	Unemployed	Primary school	Nuclear	Urban
18	54827	C.P.S.	59	M	Married	Semi- Skilled	Middle school	Nuclear	Urban
19	197537	K.	40	F	Married	Unemployed	Higher school	Nuclear	Urban
20	167836	H.K	51	F	Married	Unemployed	Graduation	Nuclear	Urban
21	456782	G.K.	44	F	Married	Professional	Post-Graduation	Nuclear	Urban
22	55683	D.S.	46	M	Unmarried	Semi-Professional	Graduation	Nuclear	Urban
23	125679	A.G.	51	F	Married	Semi-Professional	Higher secondary	Nuclear	Rural
24	143786	B.B.	59	F	Married	Semi- Skilled	Middle school	Nuclear	Urban
25	873562	G.K.	44	F	Married	Unemployed	Primary school	Nuclear	Urban
26	1265783	G.F.S.	32	M	Married	Skilled	Primary school	Nuclear	Urban
27	1546270	O.K.	47	F	Married	Professional	Graduate	Nuclear	Urban
28	69258	N.S.	35	M	Married	Semi-Professional	Graduate	Nuclear	Urban
29	455752	S.S	57	M	Married	Semi-Professional	Graduate	Joint	Urban
30	167825	F.S.	38	M	Married	Skilled	Middle school	Nuclear	Rural

S.NO.	MRD NO.	NAME INITIALS	AGE OF ONSET OF DEPRESSION (FIRST EPISODE IN YEARS)	NO. OF LIFETIME EPISODES	FAMILY HISTORY	DURATION OF CURRENT EPISODE (MONTHS)	INSIGHT	ANTIDEPRESSANT (ESCITALOPRAM) DOSE	MADRS	BASELINE-MADRS_1
1	1222980	B.S.	32	2	YES	1.5	4	20	38	38
2	1558135	J.S.	38	1	YES	6	4	20	36	36
3	60418	M.K.	42	2	YES	9	4	20	39	39
4	567821	S.K	38	2	NO	8	4	20	46	46
5	185425	T.K.	36	2	YES	6	4	20	48	48
6	784402	D.K.	41	1	NO	8	4	20	48	48
7	149117	H.S.	32	2	YES	5	4	20	52	52
8	1566683	K.K.	32	3	YES	7	4	20	38	38
9	1637529	V.N.	35	2	YES	9	4	20	42	42
10	1572453	A.D.	28	3	YES	7	4	20	38	38
11	1433253	N.K.	29	1	NO	9	4	20	40	40
12	59583	J.K.	30	2	YES	6	4	20	46	46
13	57691	K.S.	32	1	NO	1	4	20	38	38
14	52195	K.S.	36	3	YES	1.5	4	20	48	48
15	45518	K.K.	26	2	YES	1	4	20	46	46
16	1345762	A.K.	34	2	NO	9	4	20	37	37
17	456872	K.D.	32	1	NO	9	4	20	31	31
18	54827	C.P.S.	30	3	YES	7	4	20	31	31
19	197537	K.	34	2	YES	5	4	20	35	35
20	167836	H.K	35	2	YES	5	4	20	36	36
21	456782	G.K.	36	2	YES	5	4	20	31	31
22	55683	D.S.	32	1	NO	8	4	20	47	47
23	125679	A.G.	38	3	YES	12	4	20	39	39
24	143786	B.B.	34	2	NO	9	4	20	33	33
25	873562	G.K.	32	1	NO	9	4	20	33	33
26	1265783	G.F.S.	38	2	YES	6	4	20	37	37
27	1546270	O.K.	21	3	YES	5	4	20	38	38
28	69258	N.S.	25	2	YES	6	4	20	33	33
29	455752	S.S	42	2	NO	8	4	20	49	49
30	167825	F.S.	40	2	YES	10	4	20	43	43

S.NO.	MRD NO.	NAME INITIALS	t_1–4 hrs	Baseline-CADSS_1	C_1-60 mins	MODIFIED ALDERTE-1	BASELINE-MADRS_2	t_2–4 hrs	Baseline-CADSS_2	C_2-60 mins	MODIFIED ALDERETE-2	BASELINE-MADRS_3
1	1222980	B.S.	32	0	6	10	32	26	0	5	9	26
2	1558135	J.S.	32	0	4	10	32	26	0	4	10	26
3	60418	M.K.	33	0	4	10	33	25	0	4	10	25
4	567821	S.K	40	0	5	10	40	36	0	6	9	36
5	185425	T.K.	44	0	9	10	44	38	0	9	10	38
6	784402	D.K.	42	0	8	10	42	36	0	8	10	36
7	149117	H.S.	46	1	6	10	46	38	0	6	10	38
8	1566683	K.K.	32	0	6	10	32	26	0	6	10	26
9	1637529	V.N.	37	1	6	10	37	31	0	6	10	31
10	1572453	A.D.	32	0	12	10	32	28	1	10	10	28
11	1433253	N.K.	36	0	10	9	36	30	0	10	9	30
12	59583	J.K.	38	0	8	9	38	32	0	8	10	32
13	57691	K.S.	34	0	6	10	34	30	0	8	9	30
14	52195	K.S.	44	0	12	9	44	38	0	12	10	38
15	45518	K.K.	44	0	10	10	44	38	0	8	9	38
16	1345762	A.K.	29	0	4	10	32	30	0	6	10	30
17	456872	K.D.	26	0	4	10	30	26	0	4	10	26
18	54827	C.P.S.	31	0	8	10	44	41	0	8	10	41
19	197537	K.	32	1	4	10	39	35	0	6	10	35
20	167836	H.K	30	0	4	10	34	30	1	5	10	30
21	456782	G.K.	29	0	3	10	29	25	0	3	10	25
22	55683	D.S.	44	0	2	10	26	23	0	4	10	23
23	125679	A.G.	32	1	6	10	34	30	0	4	10	30
24	143786	B.B.	30	0	4	10	32	30	0	6	10	30
25	873562	G.K.	30	0	4	10	30	26	0	4	10	26
26	1265783	G.F.S.	36	0	8	10	44	41	0	8	10	41
27	1546270	O.K.	35	1	4	10	39	35	0	6	10	35
28	69258	N.S.	28	0	4	10	34	30	1	5	10	30
29	455752	S.S	45	0	2	10	36	32	0	3	10	32
30	167825	F.S.	40	0	4	10	30	26	0	4	10	26

S.NO.	MRD NO.	NAME INITIALS	t_3–4 hrs	Baseline-CADSS_3	C_3-60 mins	MODIFIED ALDERTE-3	BASELINE-MADRS_4	t_4–4 hrs	Baseline-CADSS_4	C_4-60 mins	MODIFIED ALDERTE-4
1	1222980	B.S.	20	0	5	10	20	14	0	5	10
2	1558135	J.S.	20	0	4	10	20	13	0	3	10
3	60418	M.K.	22	0	4	9	22	16	0	6	9
4	567821	S.K	32	0	5	10	32	28	0	7	10
5	185425	T.K.	31	0	8	10	31	22	1	6	10
6	784402	D.K.	30	1	7	9	30	23	0	6	9
7	149117	H.S.	30	0	5	10	30	22	0	5	10
8	1566683	K.K.	24	0	7	9	24	21	0	7	10
9	1637529	V.N.	26	0	7	9	26	20	1	6	10
10	1572453	A.D.	23	1	10	10	23	18	0	9	10
11	1433253	N.K.	24	0	8	10	24	18	0	10	10
12	59583	J.K.	26	0	8	9	26	20	0	6	10
13	57691	K.S.	24	1	6	10	24	18	0	4	9
14	52195	K.S.	32	0	10	10	32	24	0	8	10
15	45518	K.K.	30	0	8	10	30	22	0	8	10
16	1345762	A.K.	26	1	5	10	26	22	0	5	10
17	456872	K.D.	20	0	3	10	20	16	0	6	9
18	54827	C.P.S.	36	0	10	10	36	30	0	8	10
19	197537	K.	28	0	7	9	28	22	1	6	10
20	167836	H.K	26	1	4	10	26	20	0	5	10
21	456782	G.K.	22	0	2	10	22	15	0	2	9
22	55683	D.S.	21	0	4	10	21	18	1	3	10
23	125679	A.G.	24	0	3	9	24	21	0	4	10
24	143786	B.B.	26	1	5	10	26	22	0	5	10
25	873562	G.K.	20	0	3	10	20	16	0	6	9
26	1265783	G.F.S.	36	0	10	10	36	30	0	8	10
27	1546270	O.K.	28	0	7	9	28	22	1	6	10
28	69258	N.S.	26	1	4	10	26	20	0	5	10
29	455752	S.S	26	0	3	10	26	21	0	2	9
30	167825	F.S.	20	0	3	10	20	16	0	6	9

S.NO.	MRD NO.	NAME INITIALS	AGE	SEX	MARITAL STATUS	OCCUPATION	EDUCATION	TYPE OF FAMILY	LOCALITY
1	240988	N.S	32	M	Unmarried	Semi-Professional	Graduation	Nuclear	Urban
2	1360531	R.K	50	F	Married	Unemployed	Higher school	Nuclear	Rural
3	15284525	S.K.	38	F	Married	Semi- Skilled	Middle school	Nuclear	Urban
4	1282667	S.P.	32	F	Married	Unemployed	Primary school	Nuclear	Urban
5	546304	A.K	53	M	Married	Semi- Skilled	Higher school	Nuclear	Urban
6	48724	S.K	54	F	Married	Unemployed	Higher school	Nuclear	Urban
7	915133	H.A	42	F	Married	Unemployed	Graduation	Nuclear	Urban
8	1401816	G.K.	45	F	Married	Professional	Post-Graduation	Nuclear	Urban
9	1078492	A.R	42	F	Married	Unemployed	Higher school	Joint	Rural
10	65490	K.S	46	M	Married	Skilled	Primary school	Nuclear	Urban
11	704835	R.C.	39	F	Married	Professional	Graduate	Nuclear	Urban
12	1684346	A.	28	M	Married	Semi-Professional	Graduate	Nuclear	Urban
13	1647957	K.K.	55	M	Married	Professional	Graduate	Joint	Urban
14	447958	D.S.	53	M	Married	Skilled	Middle school	Nuclear	Rural
15	72845	K.	46	F	Married	Unemployed	Higher school	Nuclear	Rural
16	385667	B.K	35	F	Married	Semi-Skilled	Middle school	Nuclear	Urban
17	1215603	S.K	53	F	Married	Unemployed	Middle school	Nuclear	Urban
18	707525	M.S.	41	M	Married	Professional	Higher school	Nuclear	Urban
19	408281	J.K.	35	F	Married	Unemployed	Higher school	Nuclear	Urban
20	1268049	D.K.	56	F	Married	Unemployed	Graduation	Nuclear	Urban
21	1668937	G.K.	57	F	Married	Professional	Post-Graduation	Nuclear	Urban
22	56832	P.S.	45	M	Unmarried	Self employed	Graduation	Nuclear	Urban
23	762830	P.K.	48	F	Married	Unemployed	Higher school	Nuclear	Rural
24	538873	V.K.	45	F	Married	Semi- Skilled	Middle school	Nuclear	Urban
25	592841	M.K.	49	F	Married	Unemployed	Higher school	Nuclear	Urban
26	1284932	H.S.	42	M	Married	Skilled	Primary school	Nuclear	Urban
27	332880	K.K.	31	F	Married	Professional	Graduate	Nuclear	Urban
28	2785303	K.S	58	M	Married	Semi- Skilled	Graduate	Nuclear	Urban
29	2887434	J.S.	56	M	Married	Semi-Professional	Graduate	Joint	Urban
30	83266	R.S.	49	M	Married	Skilled	Middle school	Nuclear	Rural

S.NO.	MRD NO.	NAME INITIALS	AGE OF ONSET OF DEPRESSION (FIRST EPISODE IN YEARS)	NO. OF LIFETIME EPISODES	FAMILY HISTORY	DURATION OF CURRENT EPISODE (MONTHS)	INSIGHT	ANTIDEPRESSANT (ESCITALOPRAM) DOSE	MADRS	BASELINE-MADRS_1
1	240988	N.S	32	1	NO	8	4	20	38	38
2	1360531	R.K	38	3	YES	12	4	20	32	32
3	15284525	S.K.	34	2	NO	9	4	20	32	32
4	1282667	S.P.	32	1	NO	9	4	20	36	36
5	546304	A.K	30	3	YES	7	4	20	37	37
6	48724	S.K	34	2	YES	5	4	20	32	32
7	915133	H.A	35	2	YES	5	4	20	48	48
8	1401816	G.K.	36	2	YES	5	4	20	42	42
9	1078492	A.R	42	1	NO	8	4	20	36	36
10	65490	K.S	38	2	YES	6	4	20	39	39
11	704835	R.C.	21	3	YES	5	4	20	46	46
12	1684346	A.	25	2	YES	6	4	20	52	52
13	1647957	K.K.	42	2	NO	8	4	20	33	33
14	447958	D.S.	40	2	YES	10	4	20	32	32
15	72845	K.	36	3	YES	4	4	20	46	46
16	385667	B.K	34	1	NO	9	4	20	37	37
17	1215603	S.K	32	3	NO	7	4	20	31	31
18	707525	M.S.	30	2	YES	6	4	20	31	31
19	408281	J.K.	34	2	YES	5	4	20	45	45
20	1268049	D.K.	35	2	YES	5	4	20	36	36
21	1668937	G.K.	36	2	YES	5	4	20	31	31
22	56832	P.S.	32	3	NO	8	4	20	47	47
23	762830	P.K.	38	3	YES	12	4	20	39	39
24	538873	V.K.	34	2	NO	9	4	20	33	33
25	592841	M.K.	32	2	NO	9	4	20	37	37
26	1284932	H.S.	38	2	YES	6	4	20	38	38
27	332880	K.K.	21	3	YES	5	4	20	42	42
28	2785303	K.S	25	2	YES	6	4	20	33	33
29	2887434	J.S.	42	2	NO	8	4	20	49	49
30	83266	R.S.	40	2	YES	10	4	20	46	46

S.NO.	MRD NO.	NAME INITIALS	t_1–4 hrs	Baseline-CADSS_1	C_1-60 mins	MODIFIED ALDERTE-1	BASELINE-MADRS_2	t_2–4 hrs	Baseline-CADSS_2	C_2-60 mins	MODIFIED ALDERETE-2	BASELINE-MADRS_3
1	240988	N.S	34	0	4	10	34	32	0	3	10	32
2	1360531	R.K	29	0	3	10	29	25	0	3	10	25
3	15284525	S.K.	26	0	2	10	26	23	0	4	10	23
4	1282667	S.P.	34	1	6	10	34	30	0	4	10	30
5	546304	A.K	32	0	4	10	32	30	0	6	10	30
6	48724	S.K	30	0	4	10	30	26	0	4	10	26
7	915133	H.A	44	0	8	10	44	41	0	8	10	41
8	1401816	G.K.	39	1	4	10	39	35	0	6	10	35
9	1078492	A.R	34	0	4	10	34	30	1	5	10	30
10	65490	K.S	36	0	2	10	36	32	0	3	10	32
11	704835	R.C.	43	0	8	10	43	38	1	6	10	38
12	1684346	A.	47	0	4	10	47	41	0	4	10	41
13	1647957	K.K.	29	1	2	9	29	25	0	3	10	25
14	447958	D.S.	30	0	4	10	30	26	0	4	9	26
15	72845	K.	41	0	4	10	41	38	1	5	10	38
16	385667	B.K	34	0	4	10	34	30	0	6	10	30
17	1215603	S.K	26	0	4	10	26	22	0	4	10	22
18	707525	M.S.	28	0	8	10	28	25	0	8	10	25
19	408281	J.K.	40	1	4	10	40	34	0	6	10	34
20	1268049	D.K.	30	0	4	10	30	26	1	5	10	26
21	1668937	G.K.	29	0	3	10	29	25	0	3	10	25
22	56832	P.S.	44	0	2	10	44	40	0	4	10	40
23	762830	P.K.	37	1	6	10	37	34	0	4	10	34
24	538873	V.K.	28	0	4	10	28	24	0	6	10	24
25	592841	M.K.	34	0	4	10	34	28	0	4	10	28
26	1284932	H.S.	36	0	8	10	36	30	0	8	10	30
27	332880	K.K.	38	1	4	10	38	35	0	6	10	35
28	2785303	K.S	30	0	4	10	30	26	1	5	10	26
29	2887434	J.S.	45	0	2	10	45	40	0	3	10	40
30	83266	R.S.	44	0	4	10	44	40	0	4	10	40

S.NO.	MRD NO.	NAME INITIALS	t_3–4 hrs	Baseline-CADSS_3	C_3-60 mins	MODIFIED ALDERTE-3	BASELINE-MADRS_4	t_4–4 hrs	Baseline-CADSS_4	C_4-60 mins	MODIFIED ALDERTE-4
1	240988	N.S	28	0	4	10	28	22	0	3	10
2	1360531	R.K	22	0	2	10	22	15	0	2	9
3	15284525	S.K.	21	0	4	10	21	18	1	3	10
4	1282667	S.P.	24	0	3	9	24	21	0	4	10
5	546304	A.K	26	1	5	10	26	22	0	5	10
6	48724	S.K	20	0	3	10	20	16	0	6	9
7	915133	H.A	36	0	10	10	36	30	0	8	10
8	1401816	G.K.	28	0	7	9	28	22	1	6	10
9	1078492	A.R	26	1	4	10	26	20	0	5	10
10	65490	K.S	26	0	3	10	26	21	0	2	9
11	704835	R.C.	32	0	5	10	32	26	0	5	10
12	1684346	A.	34	0	3	9	34	26	0	3	10
13	1647957	K.K.	20	0	3	10	20	14	0	2	10
14	447958	D.S.	22	1	4	9	22	17	0	4	10
15	72845	K.	34	0	3	10	34	29	0	4	10
16	385667	B.K	26	1	5	10	26	20	0	5	10
17	1215603	S.K	18	0	3	10	18	16	0	6	9
18	707525	M.S.	20	0	10	10	20	16	0	8	10
19	408281	J.K.	28	0	7	9	28	22	1	6	10
20	1268049	D.K.	20	1	4	10	20	16	0	5	10
21	1668937	G.K.	22	0	2	10	22	14	0	2	9
22	56832	P.S.	34	0	4	10	34	28	1	3	10
23	762830	P.K.	30	0	3	9	30	20	0	4	10
24	538873	V.K.	20	1	5	10	20	16	0	5	10
25	592841	M.K.	22	0	3	10	22	16	0	6	9
26	1284932	H.S.	26	0	10	10	26	20	0	8	10
27	332880	K.K.	30	0	7	9	30	22	1	6	10
28	2785303	K.S	22	1	4	10	22	18	0	5	10
29	2887434	J.S.	36	0	3	10	36	26	0	2	9
30	83266	R.S.	34	0	3	10	34	22	0	6	9

S.NO.	MRD NO.	NAME INITIALS	AGE	SEX	MARITAL STATUS	OCCUPATION	EDUCATION	TYPE OF FAMILY	LOCALITY
1	840611	R.K.	34	Female	Married	Unemployed	Graduate	Nuclear	Urban
2	817944	S.B.	40	Female	Married	Unemployed	Graduate	Nuclear	Urban
3	49763	T.S.	31	Male	Married	Semi-Skilled	Graduate	Nuclear	Urban
4	58636	A.S.	46	Male	Married	Skilled	Higher school	Nuclear	Urban
5	498094	K.K.	28	Female	Married	Professional	Post-graduate	Nuclear	Urban
6	63407	B.D.	32	Male	Unmarried	Semi-Skilled	Higher school	Nuclear	Urban
7	1640709	M.S.	55	Male	Married	Skilled	Primary school	Joint	Rural
8	522621	R.K.	60	Female	Married	Unemployed	Higher school	Joint	Rural
9	69070	M.S.	42	Male	Married	Skilled	Graduate	Joint	Urban
10	910726	S.S.	46	Male	Married	Skilled	Higher school	Nuclear	Rural
11	668461	P.K.	50	Female	Married	Unemployed	Higher school	Nuclear	Rural
12	58857	P.S.	60	Male	Married	Skilled	Higher school	Joint	Urban
13	565318	V.S.	38	Male	Married	Semi-Skilled	Graduate	Nuclear	Urban
14	71017	S.	41	Male	Married	Semi-Skilled	Graduate	Nuclear	Urban
15	57097	K.M.	58	Female	Married	Semi-Skilled	Graduate	Nuclear	Urban
16	1600677	S.S.	36	Male	Married	Skilled	Higher school	Nuclear	Rural
17	276231	R.K.	58	Female	Married	Unemployed	Higher school	Nuclear	Urban
18	474522	S.S.	47	Male	Married	Semi-Skilled	Higher school	Nuclear	Urban
19	599487	S.K.	42	Female	Married	Unemployed	Higher school	Nuclear	Rural
20	1252130	M.A.	42	Male	Married	Professional	Post-graduate	Nuclear	Urban
21	1434621	A.K.	32	Female	Married	Unemployed	Graduate	Nuclear	Urban
22	55475	H.M.	59	Male	Married	Semi-Skilled	Higher school	Nuclear	Urban
23	784106	R.K	32	Female	Married	Unemployed	Post-graduate	Nuclear	Rural
24	662957	J.S.	52	Male	Married	Skilled	Middle school	Nuclear	Rural
25	1357596	S.S.	41	Male	Married	Skilled	Graduate	Nuclear	Urban
26	207423	M.S.	53	Male	Married	Skilled	Primary school	Nuclear	Rural
27	982002	B.D.	61	Female	Married	Unemployed	Higher school	Joint	Rural
28	1383545	K.K.	39	Female	Married	Unemployed	Higher school	Joint	Rural
29	1202264	S.K.	45	Female	Married	Unemployed	Higher school	Nuclear	Rural
30	594796	D.K.	38	Female	Married	Unemployed	Graduate	Nuclear	Urban

S.NO.	MRD NO.	NAME INITIALS	AGE OF ONSET OF DEPRESSION (FIRST EPISODE IN YEARS)	NO. OF LIFETIME EPISODES	FAMILY HISTORY	DURATION OF CURRENT EPISODE (MONTHS)	INSIGHT	ANTIDEPRESSANT (ESCITALOPRAM) DOSE	MADRS	BASELINE-MADRS_1
1	840611	R.K.	34	1	NO	9	4	20	27	-
2	817944	S.B.	37	2	YES	7	4	20	32	-
3	49763	T.S.	31	1	YES	6	4	20	29	-
4	58636	A.S.	46	1	NO	5	4	20	27	-
5	498094	K.K.	25	2	YES	6	4	20	32	-
6	63407	B.D.	32	1	NO	7	4	20	34	-
7	1640709	M.S.	35	3	YES	10	4	20	32	-
8	522621	R.K.	44	2	NO	4	4	20	30	-
9	69070	M.S.	38	2	NO	7	4	20	36	-
10	910726	S.S.	42	2	YES	8	4	20	32	-
11	668461	P.K.	42	2	YES	5	4	20	28	-
12	58857	P.S.	35	3	YES	9	4	20	38	-
13	565318	V.S.	36	2	YES	6	4	20	32	-
14	71017	S.	35	2	YES	6	4	20	28	-
15	57097	K.M.	42	2	YES	4	4	20	39	-
16	1600677	S.S.	36	1	NO	8	4	20	28	-
17	276231	R.K.	32	2	YES	6	4	20	33	-
18	474522	S.S.	44	2	YES	6	4	20	28	-
19	599487	S.K.	42	1	YES	8	4	20	38	-
20	1252130	M.A.	30	3	YES	7	4	20	32	-
21	1434621	A.K.	32	1	NO	5	4	20	27	-
22	55475	H.M.	37	3	YES	2	4	20	32	-
23	784106	R.K	32	1	YES	3	4	20	24	-
24	662957	J.S.	40	2	YES	6	4	20	29	-
25	1357596	S.S.	35	2	YES	2	4	20	28	-
26	207423	M.S.	40	2	YES	7	4	20	36	-
27	982002	B.D.	48	2	YES	4	4	20	28	-
28	1383545	K.K.	27	2	YES	5	4	20	30	-
29	1202264	S.K.	34	3	NO	6	4	20	26	-
30	594796	D.K.	38	1	NO	9	4	20	27	-

S.NO.	MRD NO.	NAME INITIALS	t_1–4 hrs	Baseline-CADSS_1	C_1-60 mins	MODIFIED ALDERTE-1	BASELINE-MADRS_2	t_2–4 hrs	Baseline-CADSS_2	C_2-60 mins	MODIFIED ALDERETE-2	BASELINE-MADRS_3
1	840611	R.K.	-	-	-	-	-	-	-	-	-	-
2	817944	S.B.	-	-	-	-	-	-	-	-	-	-
3	49763	T.S.	-	-	-	-	-	-	-	-	-	-
4	58636	A.S.	-	-	-	-	-	-	-	-	-	-
5	498094	K.K.	-	-	-	-	-	-	-	-	-	-
6	63407	B.D.	-	-	-	-	-	-	-	-	-	-
7	1640709	M.S.	-	-	-	-	-	-	-	-	-	-
8	522621	R.K.	-	-	-	-	-	-	-	-	-	-
9	69070	M.S.	-	-	-	-	-	-	-	-	-	-
10	910726	S.S.	-	-	-	-	-	-	-	-	-	-
11	668461	P.K.	-	-	-	-	-	-	-	-	-	-
12	58857	P.S.	-	-	-	-	-	-	-	-	-	-
13	565318	V.S.	-	-	-	-	-	-	-	-	-	-
14	71017	S.	-	-	-	-	-	-	-	-	-	-
15	57097	K.M.	-	-	-	-	-	-	-	-	-	-
16	1600677	S.S.	-	-	-	-	-	-	-	-	-	-
17	276231	R.K.	-	-	-	-	-	-	-	-	-	-
18	474522	S.S.	-	-	-	-	-	-	-	-	-	-
19	599487	S.K.	-	-	-	-	-	-	-	-	-	-
20	1252130	M.A.	-	-	-	-	-	-	-	-	-	-
21	1434621	A.K.	-	-	-	-	-	-	-	-	-	-
22	55475	H.M.	-	-	-	-	-	-	-	-	-	-
23	784106	R.K	-	-	-	-	-	-	-	-	-	-
24	662957	J.S.	-	-	-	-	-	-	-	-	-	-
25	1357596	S.S.	-	-	-	-	-	-	-	-	-	-
26	207423	M.S.	-	-	-	-	-	-	-	-	-	-
27	982002	B.D.	-	-	-	-	-	-	-	-	-	-
28	1383545	K.K.	-	-	-	-	-	-	-	-	-	-
29	1202264	S.K.	-	-	-	-	-	-	-	-	-	-
30	594796	D.K.	-	-	-	-	-	-	-	-	-	-

S.NO.	MRD NO.	NAME INITIALS	t_3–4 hrs	Baseline-CADSS_3	C_3-60 mins	MODIFIED ALDERTE-3	BASELINE-MADRS_4	t_4–4 hrs	Baseline-CADSS_4	C_4-60 mins	MODIFIED ALDERTE-4
1	840611	R.K.	-	-	-	-	-	-	-	-	-
2	817944	S.B.	-	-	-	-	-	-	-	-	-
3	49763	T.S.	-	-	-	-	-	-	-	-	-
4	58636	A.S.	-	-	-	-	-	-	-	-	-
5	498094	K.K.	-	-	-	-	-	-	-	-	-
6	63407	B.D.	-	-	-	-	-	-	-	-	-
7	1640709	M.S.	-	-	-	-	-	-	-	-	-
8	522621	R.K.	-	-	-	-	-	-	-	-	-
9	69070	M.S.	-	-	-	-	-	-	-	-	-
10	910726	S.S.	-	-	-	-	-	-	-	-	-
11	668461	P.K.	-	-	-	-	-	-	-	-	-
12	58857	P.S.	-	-	-	-	-	-	-	-	-
13	565318	V.S.	-	-	-	-	-	-	-	-	-
14	71017	S.	-	-	-	-	-	-	-	-	-
15	57097	K.M.	-	-	-	-	-	-	-	-	-
16	1600677	S.S.	-	-	-	-	-	-	-	-	-
17	276231	R.K.	-	-	-	-	-	-	-	-	-
18	474522	S.S.	-	-	-	-	-	-	-	-	-
19	599487	S.K.	-	-	-	-	-	-	-	-	-
20	1252130	M.A.	-	-	-	-	-	-	-	-	-
21	1434621	A.K.	-	-	-	-	-	-	-	-	-
22	55475	H.M.	-	-	-	-	-	-	-	-	-
23	784106	R.K	-	-	-	-	-	-	-	-	-
24	662957	J.S.	-	-	-	-	-	-	-	-	-
25	1357596	S.S.	-	-	-	-	-	-	-	-	-
26	207423	M.S.	-	-	-	-	-	-	-	-	-
27	982002	B.D.	-	-	-	-	-	-	-	-	-
28	1383545	K.K.	-	-	-	-	-	-	-	-	-
29	1202264	S.K.	-	-	-	-	-	-	-	-	-
30	594796	D.K.	-	-	-	-	-	-	-	-	-

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The Principal
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Ludhiana

Subject:: Approval of Plan of Thesis.

This is to inform you that the Faculty of Medical Sciences in its meeting held on 25.09.2023 has approved the plan of thesis of **Nitin Baldeep Singh Duggal**, a student of your college for **MD Psychiatry** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
Effect of ketamine on patients with moderate to severe depressive disorder .

Supervisor
Dr. Ranjive Mahajan
Prof. & Head
Dept. of Psychiatry

Co-Supervisor:-
Dr. P L Gautam
Prof. & Head
Dept. of Critical Care Medicine

Co-Supervisor:-
Dr. Navkiran S. Mahajan
Professor
Dept. of Psychiatry

The student may submit the thesis in triplicate alongwith the plan in triplicate also, to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She may be directed to attach a photocopy of this letter with the forwarding letter while submitting thesis in the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic, if any.

Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*

EFFECT OF KETAMINE ON PATIENTS WITH MODERATE TO SEVERE DEPRESSIVE DISORDER

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED IN

PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MD

In

PSYCHIATRY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

AUGUST, 2022

Dr. NITIN BALDEEP SINGH DUGGAL

DEPARTMENT OF PSYCHIATRY
DAYANAND MEDICAL COLLEGE AND HOSPITAL
LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	Effect Of Ketamine On Patients With Moderate To Severe Depressive Disorder
For the degree of	M.D PSYCHIATRY
Name of the candidate	Dr. Nitin Baldeep Singh Duggal
Supervisor	Dr. Ranjive Mahajan, Professor and Head , Department of Psychiatry, DMCH, Ludhiana
Co-supervisor(s)	Dr. P L Gautam, Professor & Head, Department of Critical Care Medicine, DMCH, Ludhiana. Dr. Navkiran S. Mahajan, Professor, Department of Psychiatry, DMCH, Ludhiana
Institution	Dayanand Medical College and Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Depressive disorder (DD) is a debilitating disease that is characterized by depressed mood, diminished interests, impaired cognitive function and vegetative symptoms. The current treatment primarily depends upon manipulation of brain monoaminergic system but with a limited efficacy. It is noteworthy that half of the suicides that occur per year world-wide are associated with DD. Recent evidence suggests that a single sub-anesthetic dose of ketamine, glutamate-modulating agent, acutely reduces depressive symptoms in approximately 70% of DD patients 24 hours after infusion. Some studies support the rapid antidepressant effect of ketamine (intravenous and intramuscular) as an adjunctive to SSRI in Moderate to severe Depressive Disorder.

Aim of Study: To compare the therapeutic efficacy of ketamine given by intravenous route versus intramuscular route in patients of DD.

Materials & methods: This randomised controlled study will be conducted in Department of Psychiatry of DMC&H, Ludhiana over a period of one year on 90 patient in age group 18-65 diagnosed with Depressive Disorder as per International Classification of Diseases (ICD-11) taking one class of antidepressant (Escitalopram 10-20 mg) for 4 weeks. They will be admitted as indoor patients and further randomised into 3 groups of 30 patients each. Group A (n=30) will receive intravenous Ketamine, Group B (n=30) will receive intramuscular Ketamine and Group C (n=30) will act as control group. The severity of depression will be assessed on Montogomery-Asberg Depression Rating Scale (MADRS).

Clinical Significance: In this study therapeutic efficacy of intravenous versus intramuscular ketamine will be assessed and compared with control group. All the three groups uses escitalopram as a part of their treatment. Early response and early remission to treatment will be assessed by measuring improvement in severity of depression on MADRS. Response will be a more than 50% improvement on MADRS.

Keywords: Depressive disorder, ketamine, therapeutic efficacy, randomised controlled study, intravenous versus intramuscular, MADRS

(Signature)	(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"EFFECT OF KETAMINE ON PATIENTS WITH MODERATE TO SEVERE DEPRESSIVE DISORDER"** exist in the Department of Psychiatry, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate himself under our supervision and guidance.

Supervisor

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Co-Supervisor's

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Place : DMC&H LUDHIANA
Date : 19/9/2022

APPROVAL PROFORMA
BY RESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Name of candidate	Nitin Baldeep Singh Duggal
Department	Psychiatry
Topic of Thesis	Effect Of Ketamine On Patients With Moderate To Severe Depressive Disorder
Likely date of appearing in PG examination	May- June 2025
Date of enrollment	4th March,2022
Name of Head of Department	Dr. Ranjive Mahajan
1) Supervisor **2) Co-Supervisor(s)**	Dr. Ranjive Mahajan Dr. P.L. Gautam Dr. Navkiran S. Mahajan
Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
Dr. Harpreet Kaur (Professor & Head, Pathology)	Mr. R K Sharma (Legal Expert)
Dr. Jaspal Singh (Professor & Head, Surgery)	Dr. Ramit Mahajan (Associate Professor, Gastroenterology)
Dr. Dinesh Gupta (Professor & Head, Medicine)	Dr. Anu Sharma (Professor, Anatomy)
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Dr. Gurpreet S Wander (Vice Principal)	Dr. Gurpreet S Wander (Vice Principal & Professor & Head, Cardiology)
	Dr. Gagandeep Singh (Secretary, Ethics Committee Professor & Head, Neurology)

Approved: Yes / ~~No~~

Dr. Sandeep Puri
Chairperson
Research Committee

Chairperson
Research Committee

Approved: Yes / ~~No~~

Prof. Arvind Malhotra
Chairperson
Ethics Committee

Ethics Committee

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

1	NAME OF THE CANDIDATE AND ADDRESS	DR. NITIN BALDEEP SINGH DUGGAL DUGGAL COTTAGE, GREEN AVENUE, NEAR OCTROI, PLAHI ROAD, PHAGWARA, PUNJAB. PIN [144401].
2	NAME OF THE INSTITUTE	DAYANAND MEDICAL COLLEGE AND HOSPITAL, LUDHIANA [PUNJAB]
3	COURSE OF STUDY AND SUBJECT	M.D PSYCHIATRY
4	DATE OF ADMISSION OF COURSE	4, MARCH,2022
5	TITLE OF THE TOPIC	"Effect Of Ketamine On Patients With Moderate To Severe Depressive Disorder."

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Depressive disorder (DD) is a debilitating disease that is characterized by depressed mood, diminished interests, impaired cognitive function and vegetative symptoms, such as disturbed sleep or appetite. DD occurs about twice as often in women than it does in men and affects one in six adults in their lifetime. The aetiology of DD is multifactorial and its heritability is estimated to be approximately 35%. In addition, environmental factors, such as sexual, physical or emotional abuse during childhood, are strongly associated with the risk of developing DD. No established mechanism can explain all aspects of the disease. However, DD is associated with alterations in regional brain volumes, particularly the hippocampus, and with functional changes in brain circuits, such as the cognitive control network and the affective–salience network. Furthermore, disturbances in the main neurobiological stress-responsive systems, including the hypothalamic–pituitary–adrenal axis and the immune system, occur in DD.[1] Its neurobiological basis is still a challenge as the current treatment primarily depends upon manipulation of brain monoaminergic system i.e., Serotonin, Norepinephrine and dopamine but with a limited efficacy. About 15-30% of DD patients are resistant to treatment.[2]

Management primarily comprises psychotherapy and pharmacological treatment.It is noteworthy that half of the suicides that occur per year world-wide are associated with DD.[3] Therefore, the search for novel drugs having fast antidepressant action is required to ameliorate the disease burden.[4]

Recent evidence suggests that a single sub-anesthetic dose of intravenous ketamine, glutamate-modulating agent, acutely reduces depressive symptoms in approximately 70% of DD patients 24 hours after infusion, but these antidepressant benefits are short-lived. However, the studies reported so far have used IV route to deliver ketamine. Little is known about the potential role of intramuscular (IM) ketamine in treatment of major depression.[5]

Ketamine, a non-competitive, N-methyl-D-aspartate glutamate-receptor(NMDAR) antagonist provides fast (within 4 hours) antidepressant effects.[6] The single sub-anesthetic dose of ketamine acts as an antidepressant within 100 minutes and its effect lasts for seven days in treatment resistant depression (TRD).[7] The sub-anaesthetic dose of ketamine partially inhibits NMDA receptors, specifically GluN2B subunits [8] and its therapeutic response is mediated by AMPA-type glutamate receptors.

In depression, there is hyper-connectivity in resting state of brain circuitry including default mode network, cognitive control and affective processing in the region of dorsal nexus. After treatment with ketamine (post-infusion 24 hours) hypersensitivity in these regions diminishes thus, suggesting its antidepressant effect.[9]

Currently, Selective Serotonin Reuptake Inhibitors [SSRIs] are the class of medication most commonly prescribed to treat depression.[10] The therapeutic actions of SSRIs have their basis on increasing deficient serotonin that researchers postulate as the cause of depression in the monoamine hypothesis. As the name suggests, SSRIs exert action by inhibiting the reuptake of serotonin, thereby increasing serotonin activity.

Unlike other classes of antidepressants, SSRIs have little effect on other neurotransmitters, such as dopamine or norepinephrine. SSRIs also have relatively fewer side effects than TCAs and MAOIs due to fewer effects on adrenergic, cholinergic, and histaminergic receptors.

SSRIs inhibit the serotonin transporter (SERT) at the presynaptic axon terminal. By inhibiting SERT, an increased amount of serotonin (5-hydroxytryptamine or 5HT) remains in the synaptic cleft and can stimulate postsynaptic receptors for a more extended period.[11,12,13]

Patients suffering from DD currently have limited treatment options, deficient in terms of both the time scale over which these medications act and the fact that a significant number of ill individuals do not respond to the currently available pharmacopeia. Some studies support the rapid actions of ketamine (IV and IM) and SSRIs when given in combination in DD. Therefore, this study will be investigating the

comparative efficacy intravenous versus intramuscular ketamine on patients suffering from DD who are already taking SSRIs. It will provide an insight regarding the rapid antidepressant efficacy and tolerability of ketamine as an adjunct to usual treatment.

6.2 REVIEW OF LITERATURE

Domino EF et al [14] first studied ketamine, a phencyclidine derivative then known as CI-581 in 20 volunteers from prison population and established its efficacy as dissociative anesthetic with fast onset of action and limited duration of action in 1965.

Krystal JH et al [15] studied behavioral, cognitive, neuroendocrine, and physiological effects of sub- anesthetic doses of ketamine hydrochloride in nine healthy human subjects. Amongst other findings, note was also made of dose-dependent alteration of mood states following ketamine administration. Subjects experienced a high, a euphoric feeling that made for a pleasant experience. Ketamine at low doses was also found to have anxiolytic effect.

Trullas and Skolnick [16] findings indicate that the NMDA receptor complex may be involved in the behavioral deficits induced by inescapable stress, and that substances capable of reducing neurotransmission at the NMDA receptor complex may represent a new class of antidepressants.

Further studies demonstrated anti-depressant like actions of other NMDA antagonist agents i.e. CGP 397849 and CCP 39551 memantine and eliprodil, an NMDA antagonist acting through polyamine coupled sites.

A review conducted by **Skolnick et al** [17] in 1996 concluded three consistent findings that clearly demonstrated the role of NMDA receptors in depression. Chronic treatment with functional NMDA antagonists led to down-regulation of cortical beta adreno-receptors. Cortical beta adreno-receptor down-regulation is a consistent finding with antidepressant use. Chronic anti-depressant treatment produced adaptive changes in radio-ligand binding to NMDA receptors. Functional NMDA receptor antagonists demonstrated anti-depressant like actions in preclinical animal studies.

ROLE OF KETAMINE IN DEPRESSION-

Berman et al.,[5] in 2000 conducted a placebo controlled, double blinded trial to assess the treatment effects of a single dose of ketamine versus placebo in 7 patients with depression as per DSM-IV.

Patients underwent two treatment days separated by at least 1 week. A saline solution alone or containing ketamine hydrochloride (total dose of 0.5 mg/kg) was infused over 40 min.

Four participants were randomly assigned to receive ketamine (0.5 mg/kg) prior to placebo infusion. Ratings included the Hamilton Depression Rating Scale (HDRS; baseline as well as 80 min, 230 min, 24 hours, 48 hours, and 72 hours after starting infusion), Beck Depression Inventory (BDI; baseline as well as 10, 40, and 110 min after infusion), Visual Analog Scales score for intoxication “high” (VAS-high; baseline as well as 10, 40, 80, and 110 min after infusion). It was observed that intravenous ketamine produced significant greater reduction on HDRS score, thus suggesting its potential role in NMDA receptor modulation in depression.

Zarate et al.,[18] in 2006 conducted a randomized, placebo- controlled, double blind crossover study on 18 subjects with TRD to determine the rapid anti- depressant effect of ketamine. Following a 2-week drug-free period, 18 subjects with MDD (DSM-IV criteria) received intravenous infusions of saline solution and 0.5 mg/kg of ketamine hydrochloride, 1 week apart. Patients were randomly assigned to the order in which they received the 2 infusions via a random-numbers chart. The infusions were administered over 40 minutes via an infusion pump. Subjects were rated 60 minutes prior to the infusion and at 40, 80, 110, and 230 minutes, as well as 1, 2, 3, and 7 days, after the infusion. Rating scales included the 21-items HDRS, which was the primary outcome measure, and the secondary outcome measure was Beck Depression Inventory (BDI). The study indicated significant improvement for ketamine over placebo at 110 minutes through 7 days. Of the 17 subjects treated with ketamine, 71% met response and 29% met remission criteria the day following ketamine infusion. Thirty-five percent of subjects maintained response for at least 1 week.

Predictors of response to Ketamine in Depression-

Cusin et al., in 2016 [19] assessed the safety and antidepressant efficacy of repeated-dose ketamine as an augmentation to ongoing

antidepressant pharmacotherapy in outpatients with TRD. Fourteen patients with treatment- resistant depression received augmentation with six open label intravenous ketamine infusions over 3 weeks. For the first three infusions, ketamine was administered at a dose of 0.5mg/kg over 45minutes; the dose was increased to 0.75mg/kg over 45minutes for the subsequent three infusions. The primary outcome measure was response as measured on Hamilton Depression Rating Scale–28 items. Results revealed there was a decrease in HAM-D28 scores that approached statistical significance ($t(13)=2.14$, $p=0.052$) with a medium effect size (Cohen's $d=0.48$) from Baseline 0 to Infusion 3. In contrast, from Infusion 3 to Infusion 6, there was a statistically significant difference in HAM-D28 scores ($t(13)=3.79$, $p=0.002$) and a large effect size ($d=1.01$).

Chilukuri, et al in 2014 [20] compared the safety, tolerability and efficacy of I.M. versus I.V. infusion of ketamine in Major Depression Disorder . It was a randomized open label parallel group study in a tertiary care teaching hospital. Study sample consisted of 27 subjects having major depression divided randomly into three groups of nine subjects each. Ketamine administered to each group in the dose of 0.5 mg/kg as an I.V. infusion, as 0.5 mg/kg I.M. or 0.25 mg/kg I.M. respectively. Depression rated on the Hamilton Depression Rating Scale (HAM-D) before the injection, two hours later, the next day, and after three days. Data analyzed using the Statistical Package for Social Sciences (SPSS). Mean age of the sample was 36.81 years (SD 11.815). Two hours after the injection, HAM-D fell by 58.86%, 60.29% & 57.36% in each group respectively. The improvement was sustained for next three days. Adverse effects noticed were rare, of mild nature and transient, lasting less than an hour.

Phillips et al., in 2019 [21] compared the antidepressant effects of a single ketamine infusion; a repeated ketamine infusions, and prolongation of response with maintenance infusions. Forty-one participants with TRD completed a single-site randomized double-blind crossover comparison of single infusions of ketamine and midazolam (an active placebo control). After relapse of depressive symptoms,

participants received a course of six open- label ketamine infusions administered thrice weekly over 2 weeks. Responders, classified as those participants who had a ≥50% decrease in their scores on the Montgomery-Åsberg Depression Rating Scale (MADRS), received four additional infusions administered once weekly (maintenance phase). Compared with midazolam, a single ketamine infusion elicited a significantly greater reduction in depressive symptoms at the primary efficacy endpoint (24 hours post infusion). Fifty-nine percent of participants met response criteria after repeated infusions, with a median of three infusions required before achieving response. Participants had no further change in MADRS scores during weekly maintenance infusions. This study indicated that repeated ketamine infusions have cumulative and sustained antidepressant effects. Reductions in depressive symptoms were maintained among responders through once-weekly infusions.

Ketamine in augmentation of antidepressants

Meta-analysis by **Romeo et al., in 2015** [22] suggested that ketamine has rapid anti-depressive effect during one week, especially in unipolar depressive disorder. They searched databases through December 2013, without limits on year of publication. Six randomized, double-blind and placebo controlled trials of ketamine in major depression (n=103 patients) were identified. Authors were contacted. Standardized mean differences (SMD) were calculated between the depression scores in ketamine and placebo groups at days 1, 2, 3,4, 7 and 14. The results indicated that ketamine has an overall anti-depressive efficacy from day 1 to day 7 (SMD=- 0.36, 95% CI: -0.65 to- 0.08, p=0.01).

Studies showing insignificant results of Ketamine

Ionescu et al., in 2019 [23] conducted a double-blind, placebo controlled study to examine the short term and long-term antidepressant efficacy of repeated dose (0.5 mg/kg) ketamine augmentation compared to placebo in medicated, TRD outpatients with chronic suicidal ideations. 26 patients were randomized to receive six 45 min intravenous infusions of either ketamine (0.5 mg/kg) or saline placebo, over three weeks (two infusions per week). Depression and suicidal ideations

were assessed at baseline, 240 min post infusion, and during a three-month follow-up phase. The analysis of depression (primary outcome; HDRS total score) and suicidal ideation (SI) (secondary outcome; C-SSRS SI score and C-SSRS SI intensity rating), the intent-to-treat (ITT) model was utilized to include all patients. Their results showed that there were no statistically significant differences in HDRS total scores between the ketamine and placebo groups across infusions ($p=0.47$). Also no group differences between ketamine vs. placebo on C-SSRS SI score or SI intensity rating were observed ($p=0.32$).

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6.3 AIMS AND OBJECTIVES OF THE STUDY

1. To compare the therapeutic efficacy of ketamine given by intravenous route versus intramuscular route in patients of depressive disorder(DD).

7. MATERIALS AND METHODS

Study will be conducted for a period of one year on patients diagnosed as Depressive Disorder presenting to DMC&H, Ludhiana

7.1 Source of Data

SAMPLE COLLECTION- This study will comprise of 90 patients in age group 18-65 diagnosed with Depressive Disorder as per International Classification of Diseases (ICD-11) taking one class of antidepressant (Escitapram 10-20 mg) for at least 4 weeks. After obtaining informed consent they will be admitted as indoor patients and further randomised into 3 groups of 30 patients each. Group A will comprise of 30 patients that will receive intravenous Ketamine, Group B (n=30) will receive intramuscular Ketamine and Group C (n=30) will act as control group.

7.2 METHOD OF COLLECTION OF DATA

INCLUSION CRITERIA

- Patient seeking treatment at the department of psychiatry, Dayanand Medical College & Hospital (DMCH), Ludhiana.
- Both males and females aged 18-65 years.
- Primary diagnosis of Depressive disorder without psychotic features based on ICD-11.
- Diagnosis of moderate-severe DD defined by MADRS ≥ 20.
- Patient who are taking escitalopram 10-20 mg for at least 4 weeks.
- Medically stable for study participation

EXCLUSION CRITERIA-

- Any other major psychiatric disorder in patients of Depressive Disorder.
- History of any known uncontrolled medical condition.
- Women who are pregnant or lactating.
- Patient who have not given consent for the study.

- Untreated hypertension (Systolic BP>140mmHg and/or Diastolic BP>90mmHg).

Methodology:

The study will be conducted on 90 patients diagnosed as Depressive Disorder as per International Classification of Diseases (ICD-11) taking atleast one class of antidepressant (escitalopram 10-20 mg) for a minimum period of 4 weeks presenting to Department of Psychiatry, DMC&H Ludhiana. To be eligible, patients had to meet the inclusion criteria and provide written informed consent before enrolment.

STUDY DESIGN-

The study is a randomised, double blinded, placebo controlled, pre and post-intervention assessment study carried out in 90 patients. Patients meeting the inclusion criteria will be randomly allocated into three groups.

Group-A subjects will receive ketamine hydrochloride (0.5 mg/kg) intravenous infusion dissolved in 100 ml normal saline via infusion pump over 40 minutes, two infusions per week for two weeks as augmentation to the ongoing antidepressant regimen.

Group-B subjects will receive ketamine hydrochloride (0.5 mg/kg) intramuscular two injections per week for two weeks as augmentation to the ongoing antidepressant regimen.

Group-C subjects will act as control group who will not receive any ketamine.

The severity of depression will be assessed on MADRS.

Patients will undergo prospective observation. Vitals (blood pressure, heart rate etc.,) will be monitored every 5 minutes throughout the time of infusion and every half hourly for 2 hours after infusion. The clinical response to ketamine administration in depressive patients will be assessed by Montgomery-Asberg Depression Rating Scale(MADRS) pre-infusion and post-infusion 4 hourly . The patients will be discharged after assessing them on Modified Aldrete Score. Thereafter, subjects will be followed up for two weeks.

Patients will be informed that they are free to withdraw from the study at any time without ramifications on their relationship with the healthcare provider.

TOOLS-

MADRS- It was developed by SA Montgomery and M Asberg in 1979 with the aim of constructing a scale which would be sensitive to treatment effects of anti- depressants. It is a 10 item diagnostic questionnaire used to measure the severity of depressive episodes in patients with mood disorders. The items are rated on a continuum of 0-6.The questionnaire includes questions on following symptoms –

1. Apparent sadness
2. Reported sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

The interpretation of scale is as follows-

- **0-6**- Normal/ Symptoms absent
- **7-19**- Mild Depression
- **20-34**- Moderate Depression
- **>34**- Severe Depression

CLINICIAN-ADMINISTERED DISSOCIATIVE STATES SCALE (CADSS) It is a reliable and valid instrument for the measurement of present-state dissociative symptomatology. The CADSS is a 27-item scale with 19 subject-rated items and 8 items scored by an observer. The subjective component consists of 19 items which are administered by a clinician who begins each question with the phrase “at this time” and then reads the item to the subject. The subject then endorses one of a range of possible responses: 0 = not at all, 1 = slightly, 2 =

moderately, 3 = considerably, 4 = extremely. The subject's response on this 0 to 4 scale is recorded and the clinician moves on to the next item. The observer component consists of eight behavioral items which have been noted in the clinical literature as behaviors consistent with the presence of a dissociative state. The high Cronbach alpha values identified in study on ketamine effects suggests that the CADSS is an internally consistent instrument for evaluating ketamine-induced dissociation in clinical trials in anxiety, although it does not capture symptoms such as thought disorder.

MODIFIED ALDRETE SCORING: The modified Aldrete score is used to evaluate patients from the Post Anaesthesia Care Unit (PACU), with the purpose to check whether they can be safely discharged. The score accounts for consciousness, mobility, breathing, circulation, tegument color and O2 saturation. The total modified Aldrete score values range from 0 to 12. Scores closer to 0 indicate that the patient is closest to the anesthesia state. Scores of 9 and above indicate that the patient can be discharged and the closer the score is to 12, the higher the chances for all anestethic, regardless of administering method, to have worn off.

OUTCOME

Primary outcome measures will be early response and early remission to treatment by improvement in severity of depression on MADRS. Response will be a more than 50% improvement MADRS.

Secondary outcome measure will be decrease in suicidal ideation and adverse events in CADSS.

STATISTICAL ANALYSIS

Data will be described in terms of range; mean ±standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. To determine whether the data is normally distributed, a Kolmogorov-Smirnov test will be used. Comparison of quantitative variables between the study groups will be done using ANOVA and using Kruskal-Wallis Test with post hoc Tukey's for independent samples for parametric and non-parametric data respectively. For comparing categorical data, Chi square ($\chi 2$) test

will be performed and fisher exact test was used when the expected frequency is less than 5. A probability value (p value)less than 0.05 will be considered statistically significant.All statistical calculations will be done using (Statistical Package for the Social Science) SPSS 21version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

YES

The patients will be given ketamine via intravenous and intramuscular route twice weekly for two weeks

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Attached herewith.

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PROFORMA

S. No.

DATE-

NAME AGE GENDER

MRD NO.

MARITAL STATUS

EDUCATION OCCUPATION/LOSS OF FUNCTION INCOME

TYPE OF FAMILY- JOINT/NUCLEAR/LIVING ALONE

ADDRESS

CONTACT NO.

AGE OF ONSET OF DEPRESSION

DURATION OF ILLNESS /COURSE OF ILLNESS

TIME BETWEEN ONSET OF SYMPTOMS AND SEEKING FIRST MEDICAL ADVICE

SPECIFIER OF DEPRESSION

INSIGHT GRADE

NUMBER OF ANTIDEPRESSANTS- MONOTHERAPY/POLYTHERAPY

TYPE OF ANTIDEPRESSANT -

COMPLIANCE

FAMILY HISTORY OF DEPRESSION

FAMILY HISTORY OF ANY MENTAL ILLNESS EXCEPT DEPRESSION

P/H/O SUICIDAL IDEATION/BEHAVIOUR/ATTEMPT (ELABORATE IF ANY)

F/H/O SUICIDE

MADRS- SEVERITY SCORE

- **0-6**- Normal
- **7-19**- Mild Depression
- **20-34**- Moderate Depression
- **>34**- Severe Depression

CLINICIAN-ADMINISTERED DISSOCIATIVE STATES SCALE (CADSS)- TOTAL SCORE

MODIFIED ALDRETE SCORING- TOTAL SCORE

INFORMED PATIENT CONSENT

Date: _____

I……..D/o, W/o, S/o……. am willing to participate in the study **"EFFECT OF KETAMINE ON PATIENTS WITH MODERATE TO SEVERE DEPRESSIVE DISORDER"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

……. ……

Signature of the Witness Signature of the patient

Name:

Signature of Candidate **Signature of Supervisor**

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____
निवासी _____
इस शोधकार्य "**EFFECT OF KETAMINE ON PATIENTS WITH MODERATE TO SEVERE DEPRESSIVE DISORDER**" में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____	_____
गवाह के हस्ताक्षर	रोगी के हस्ताक्षर/अंगूठे का निशान
नाम:	नाम:

_____
अन्वेषक के हस्ताक्षर

_____
विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

“EFFECT OF KETAMINE ON PATIENTS WITH MODERATE TO SEVERE DEPRESSIVE DISORDER” ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____ _____

ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

_____

ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____

ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ